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(71) Applicant: ORTHO PHARMACEUTICAL CORPORATION [US/US]; U.S. Route #202, P.O. Box 300, Raritan, NJ (US).

(72) Inventors: COSTANZO, Michael, J.; 14 Breckenridge Drive, Ivyland, PA 18974 (US). HOEKSTRA, William, J.; 2047 Stone Ridge Lane, Villanova, PA 19085 (US). MARYANOFF, Bruce, E.; 4029 Devonshire Drive, Forest Grove, PA 18922 (US).

(74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).

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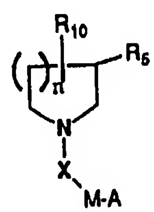
(57) Abstract

Carboxamide derivatives of pyrrolidine, piperidine, and hexahydroazepine of formula (I) are disclosed as useful in treating platelet-mediated thrombotic disorders.



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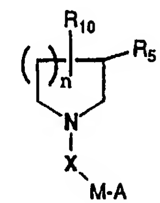
CARBOXAMIDE DERIVATIVES OF PYRROLIDINE, PIPERIDINE, AND HEXAHYDROAZEPINE FOR THE TREATMENT OF THROMBOSIS DISORDERS

BACKGROUND OF THE INVENTION

Platelet aggregation constitutes the initial hemostatic response to curtail bleeding induced by vascular injury. However, pathological extension of this normal hemostatic process can lead to thrombus formation. The final, common pathway in platelet aggregation is the binding of fibrinogen to activated, exposed platelet glycoprotein IIb/IIIa (GPIIb/IIIa). Agents which interrupt binding of fibrinogen to GPIIb/IIIa, therefore, inhibit platelet aggregation. These agents are, therefore, useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, unstable angina, reocclusion following thrombolytic therapy and angioplasty, inflammation, and a variety of vaso-occlusive disorders. The fibrinogen receptor (GPIIb/IIIa) is activated by stimuli such as ADP, collagen, and thrombin exposing binding domains to two different peptide regions of fibrinogen: α-chain Arg-Gly-Asp (RGD) and γ-chain His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val (HHLGGAKQAGDV, γ400-411). Since these peptide fragments themselves have been shown to inhibit fibrinogen binding to GPIIb/IIIa, a mimetic of these fragments would also serve as an antagonist. In fact, prior to this invention, potent RGD-based antagonists have been revealed which inhibit both fibrinogen binding to GPIIb/IIIa and platelet aggregation e.g., Ro-438857 (L. Alig, *J. Med. Chem.* **1992**, *35*, 4393) has an IC_{50} of 0.094 μM against in vitro thrombin-induced platelet aggregation. Some of these agents have also shown *in vivo* efficacy as antithrombotic agents and, in some cases, have been used in conjunction with fibrinolytic therapy e.g., t-PA or streptokinase, as well (J. A. Zablocki, *Current Pharmaceutical Design* **1995**, *1*, 533). As demonstrated by the results of the pharmacological studies described hereinafter, the compounds of the present invention show the ability to block fibrinogen binding to isolated GPIIb/IIa (IC_{50}'s 0.0002-1.39 μM), inhibit platelet aggregation *in vitro* in the presence of a variety of platelet stimuli (0.019-65.0 μM vs. thrombin), and furthermore, inhibit *ex vivo* platelet aggregation in animal models. Additionally, these agents exhibit efficacy in animal thrombosis models as their progenitors had shown ("Nipecotic Acid Derivatives As Antithrombotic Compounds," application Serial No. 08/213772, filed March 16, 1994). The compounds of the present invention show efficacy as antithrombotic agents by virtue of their ability to prevent platelet aggregation. Additionally, because the compounds of this invention inhibit integrin-mediated cell-cell or cell-matrix adhesion, they may also be useful against inflammation, bone resorption, tumor cell metastasis, etc. (D. Cox, *Drug News&Perspectives* **1995**, *8*, 197).

DISCLOSURE OF THE INVENTION

The present invention is directed to compounds represented by the following general formula (I):

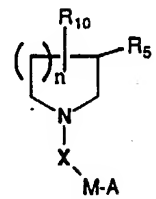


(I)

wherein A, X, M, R_5, R_{10}, and n are as hereinafter defined. These platelet aggregation inhibitors are useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and angioplasty, inflammation, unstable angina, and a variety of vaso-occlusive disorders. These compounds are also useful as antithrombotics used in conjunction with fibrinolytic therapy (e.g., t-PA or streptokinase). Pharmaceutical compositions containing such compounds are also part of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

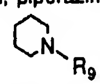
More particularly, the present invention is directed to compounds of the following formula (I):



(I)

wherein M is $(CH_2)_m$ or piperidin-1-yl;

wherein A is selected from any of piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, NHR^2, or



wherein R_9 is selected from any of H, alkyl, CH(NH), CMe(NH) or acyl, preferably R_9 is hydrogen;

wherein R_{10} is H or $C(O)N(R^1)YZ$

wherein R_1 is selected from H or cycloalkyl;

wherein R^2 is selected from any of H, alkyl or acyl. Preferably, R^2 is hydrogen;

wherein R_5 is H or $C(O)NHQ(CHW)_rCO_2R_8$; wherein Q is selected from CH_2, CH-aryl, CH-heteroaryl, CH-substituted-heteroaryl or CH-alkyl; preferably Q is CH_2, CH-substituted-heteroaryl or CH-heteroaryl; W is selected from H or $N(R_6)T\text{-}R_7$, preferably W is H when Q is CH, and $N(R_6)\text{-}T\text{-}R_7$ when Q is CH_2; wherein R_6 is selected from any of H, alkyl or acyl; preferably R_6 is hydrogen, T is selected fron C(O), C(N-CN) or SO_2, preferably T is C(O) and R_7 is selected from any of alkyl, aryl, aralkyl, alkoxy, or aminoalkyl; and R_8 is selected from H, alkyl or aralkyl; preferably R_8 is H.

wherein m is the integer 1, 2, or 3. Preferably m is 1 or 2;

wherein X is selected from any of C(O), C(O)O, C(O)NH, CH_2, or SO_2;

wherein n is the integer 1, 2, or 3;

wherein r is 0 or 1;

wherein R^1 is selected from H or cycloalkyl;

wherein Y is selected from any of $(CH_2)_p$, $CH(R^3)(CH_2)_q$, $(CH_2)_qCH(R^3)$, $(CH(COR^4)CH_2)_q$, $(CH_2)_qCHOH$ or piperidine-3-carboxylic acid; with the proviso that when Y is $(CH_2)_p$ and p is 2, X is other than C(O) or when X is C(O) then either R^1 is other than H or R^2 is other than H, and with the proviso that when Y is $(CH(CO_2R^4)CH_2)_q$ X is other than C(O) or CH_2;

wherein p is 2 or 3;

wherein q is 1, 2, or 3. Preferably, q is 1.

wherein R^3 is alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, aralkyl or heteroaryl;

wherein R^4 is H or alkyl or cycloalkyl. Preferably, R^4 is hydrogen.

wherein Z is CO_2H, CO_2alkyl, SO_3H, PO_3H_2 , or 5-tetrazole; provided that at least one of R_5 and R_{10} is hydrogen;

or the enantiomer or the pharmaceutically acceptable salt thereof.

Preferably, the group $C(O)N(R^1)YZ$ is attached to the ring carbon of the central azacycle at the 3- or 4-position (4-position when larger than a five-membered ring), and most preferably the 3-position.

As used herein, unless otherwise noted alkyl and alkoxy whether used alone or as part of a substituent group, include straight and branched chains having 1-8 carbons. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, *n*-hexyl, 2-hexyl and 2-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. Cycloalkyl groups contain 5-8 ring carbons and preferably 6-7 carbons.

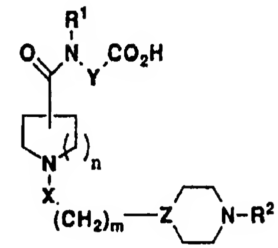
The term "aryl", "heteroaryl" or "substituted heteroaryl" as used herein alone or in combination with other terms indicates aromatic or heteroaromatic groups such as phenyl,naphthyl, pyridyl, thienyl, furanyl, or quinolinyl wherein the substituent is an alkyl group. The term "aralkyl" means an alkyl group substituted with an aryl group.

The term "acyl" as used herein means an organic radical having 2-6 carbon atoms derived from an organic acid by removal of the hydroxyl group.

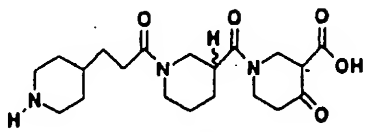
The compounds of the present invention may also be present in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salt generally takes a form in which the nitrogen on the 1-piperidine (pyrrolidine, piperazine) substituent is protonated with an inorganic or organic acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benezenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, *p*-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic.

Particularly preferred compounds of the present invention include those compounds shown in Table I, where "Subst" indicates the position of attachment of the group $C(O)N(R^1)YCO_2H$ to the central azacycle and where the letter "R" after the numeral "3" indicates the absolute configuration (Cahn-Ingold-Prelog rules). Those numerals not having any configuration specified are racemic mixtures.

TABLE I



#	Subst	m	n	X	R^1	R^2	Y	Z
1	3	2	2	C(O)	H	H	$CH(Ph)CH_2$	CH
2	3	1	2	NHCO	H	H	CH_2CHMe	CH
3	3	1	2	OC(O)	H	H	(*R*)-$CH(CO_2Me)CH_2$	CH
4	3	2	1	C(O)	H	H	$CH(3\text{-}Me\text{-}Ph)CH_2$	CH
5	4	2	2	C(O)	H	H	$CH(Me)CH_2$	CH
6	4	2	2	C(O)	H	H	$CH(4\text{-}CO_2H\text{-}Ph)CH_2$	CH
7	3	2	2	C(O)	H	Me	CH_2CH_2	CH
8	See structure							
9	3	2	2	C(O)	H	H	$CH(Me_3Si\text{-}ethynyl)CH_2$	CH
10	See structure							
11	3R	2	2	CO	H	H	$CH_2CH(OH)$	CH
12	3	2	2	SO_2	H	H	CH_2CH_2	CH
13	See structure							
14	3	2	2	CO	H	Me	$CH(3,4\text{-}OCH_2O\text{-}Ph)CH_2$	N
15	3	2	2	CO	H	Me	$CH(3\text{-}quinolinyl)CH_2$	N
16	3R	2	2	CO	H	H	*S*-$CH(3,4\text{-}OCH_2O\text{-}Ph)CH_2$	CH
17	3	2	3	CO	H	H	$CH(3\text{-}quinolinyl)CH_2$	CH
18	3R	2	2	CO	H	H	*S*-$CH(3\text{-}quinolinyl)CH_2$	CH
19	3R	2	2	CO	H	H	*S*-$CH(t\text{-}butylethynyl)CH_2$	CH
20	3	2	2	CH_2	H	H	*S*-$CH(3,4\text{-}OCH_2O\text{-}Ph)CH_2$	CH
21	3R	2	2	CO	H	H	*S*-$CH(3\text{-}pyridyl)CH_2$	CH



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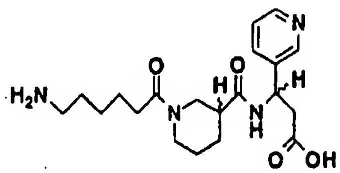

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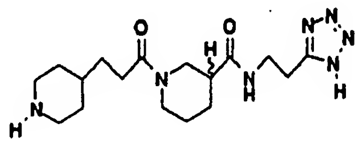

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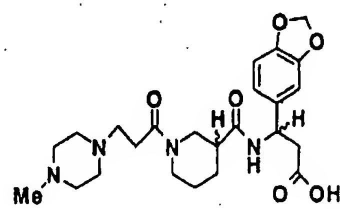

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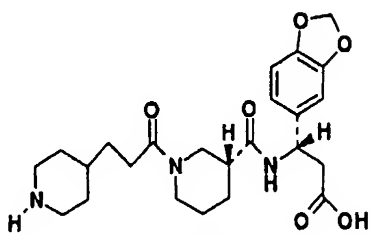

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The compounds of the invention wherein R_5 is H, R_{10} is $C(O)N(R^1)YZ$, M is $(CH_2)m$ and A is piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl or NHR^2 may be prepared as shown in Scheme AA. In this scheme nipecotic acid allyl ester (either the racemic mixture or either separate enantiomer) may be treated with resin-bound 4-piperidinepropionic acid in the presence of DIC/HOBT and a tertiary amine. The allyl ester is then removed via palladium-mediated catalysis and the iterative coupling process continued to give final product upon saponification with potassium trimethylsilanolate (e.g., compound **1**). By analogy, urea and urethane-based replacements for the tertiary amide (compounds **2** and **3**) were prepared by reaction of solid-supported amine (alcohol) with *p*-nitrophenylchloroformate and then ethyl nipecotate (S. M. Hutchins, *Tetrahedron Lett.* **1994**, *35*, 4055).

Three-substituted 3-aminopropionic acid ester intermediates were prepared utilizing a modified Knoevenagel procedure (Scheme AG; E. Profft, *J. Prakt. Chem.* **1965**, *30*, 18) followed by Fischer esterification of the carboxylic acid product (when not commercially-available). These intermediates were prepared in enantiomerically-enriched form by penicillin amidase resolution of racemic phenylacetamides such as intermediate AG3 (V. A. Soloshonok, *Tetrahedron: Asymmetry* **1995**, *6*, 1601). Here, the undesired R-enantiomer is hydrolyzed by amidase while the desired S-enantiomer retains the phenylacetyl group. Resolutions may also be performed on the (-)-ephedrine salts of racemic three-substituted 3-N-Boc-aminopropionic acids as published (J. A. Zablocki, *J. Med. Chem.* **1995**, *38*, 2378). Ethyl nipecotate and ethyl isonipecotate are commercially-available intermediates.

Synthesis of 5- and 7-membered ring analogues of nipecotamides (**4** and **17**, respectively) were prepared by solid-phase synthesis using methyl pyrrolidine-3-carboxylate and methyl hexahydroazepine-3-carboxylate intermediates for the analogous conversion of AA2 to AA3 (Scheme AA). Methyl pyrrolidine-3-carboxylate and methyl hexahydroazepine-3-carboxylate were prepared as published (H. Rapoport, *J. Org. Chem.* **1974**, *39*, 893). For example, N-benzyl hexahydroazepin-2-one was reacted with lithium diisopropylamide/diethylcarbonate and this product then reduced with lithium aluminum hydride to afford N-benzyl-3-hydroxymethyl-hexahydroazepine. The benzyl group was removed by hydrogenolysis (H_2, Pd-C, MeOH), the nitrogen protected (di-*t*-butyldicarbonate/sodium hydroxide), and the alcohol oxidized with chromium trioxide to give N-Boc-hexahydroazepine-3-carboxylic acid. The Boc group was removed concomitant with carboxylate esterification using HCl/MeOH to afford methyl hexahydroazepine-3-carboxylate.

Piperazine analogs were prepared, as exemplified in Scheme AB, as published (S. G. Gilbreath, *J. Am. Chem. Soc.* **1988**, *110*, 6172). Tetrazoles (**13**) were prepared from the corresponding nitriles using azidotrimethylsilane/dibutyltin oxide as published (Scheme AC; S. J. Wittenberger, *J. Org. Chem.* **1993**, *58*, 4139). Here, the nitrile precursor AC2 was prepared by standard amide bond coupling with 3-aminopropionitrile, and reduced on the final synthetic step using platinum

dioxide-mediated hydrogenation (W. J. Hoekstra, *J. Med. Chem.* **1995**, *38*, 1582).

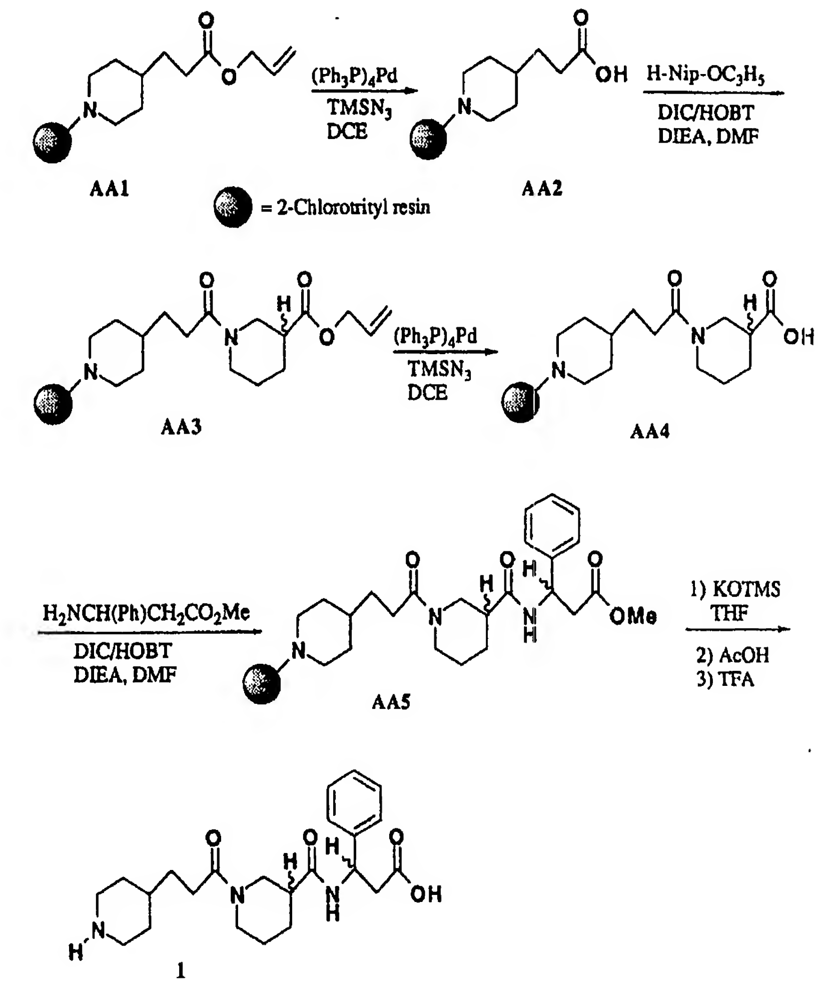
N-Methylpiperidine analogues can be prepared by Fmoc-based solid-phase peptide synthesis techniques as shown in scheme AD (P. Sieber, *Tetrahedron Lett.* **1987**, *28*, 6147). The Fmoc protecting groups were cleaved by 20% piperidine/DMF, couplings were effected using DIC/HOBT/DMF, and final products were removed from the resin with 95% TFA.

Sulfonamide **12** was prepared as shown in Scheme AE. Intermediate AE1 was isolated in two steps from 4-pyridineethanesulfonic acid by hydrogenation/protection as described (J. I. DeGaw, *J. Heterocyclic Chem.* **1966**, *3*, 90), and then chlorinated using standard thionyl chloride conditions (P. J. Hearst, *Org. Syn.* **1950**, *30*, 58) to give AE2. Intermediate AE2 was then carried forward to final product using standard solution-phase synthesis (W. J. Hoekstra, *J. Med. Chem.* **1995**, *38*, 1582).

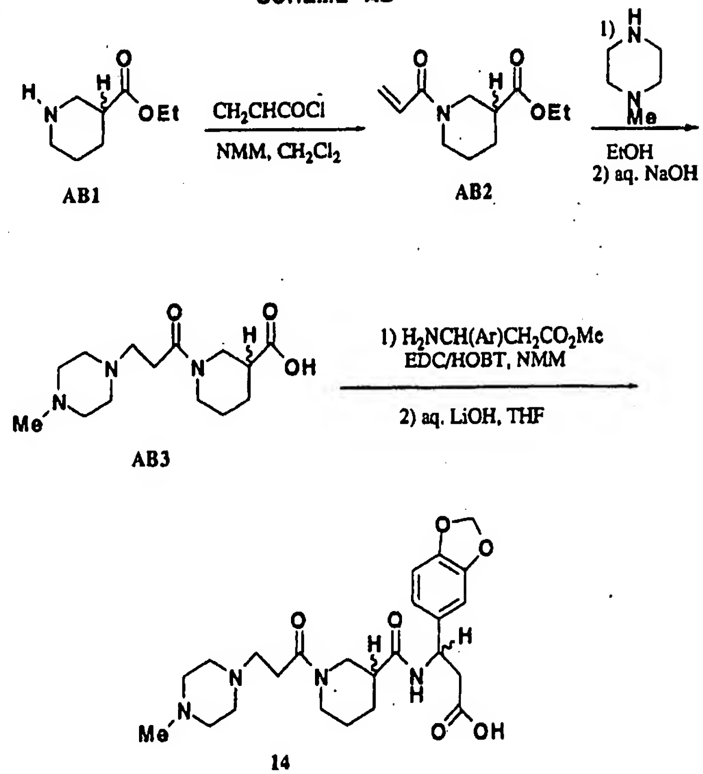
Piperidinepropyl-nipecotamide **20** was prepared as shown in Scheme AF. Ester AF1 was Boc-protected using standard Boc-ON conditions (D. S. Tarbell, *Proc. Natl. Acad. Sci. USA* **1972**, *69*, 730), and then reduced to its corresponding primary alcohol with DIBAL-H/THF (E. Winterfeldt, *Synthesis* **1975**, 617) to give intermediate AF2. This compound was converted to its corresponding tosylate AF3 using *p*-TsCl (L. F. Awad, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1587). Ethyl nipecotate was then alkylated with intermediate AF3 using standard conditions (benzene/heat; I. Seki, *Chem. Pharm. Bull. Jpn.* **1970**, *18*, 1104).

Enantiomerically-enriched R-(-)-nipecotic acid ethyl ester was isolated by chiral resolution of racemic material as its corresponding D-tartaric acid salt (A. M. Akkerman, *Rec. Trav. Chim. Pays-Bas* **1951**, *70*, 899)

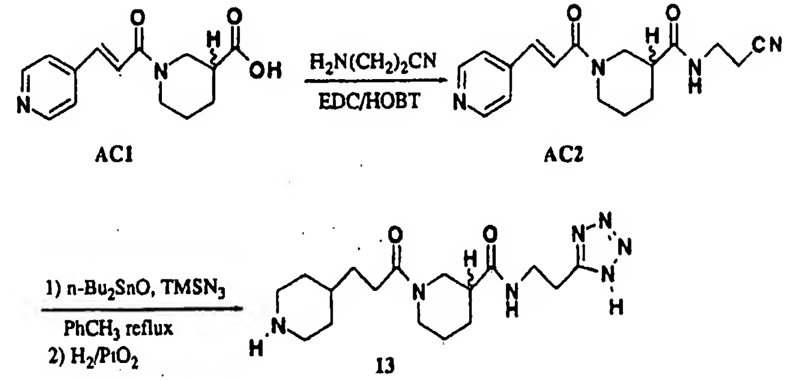
SCHEME AA



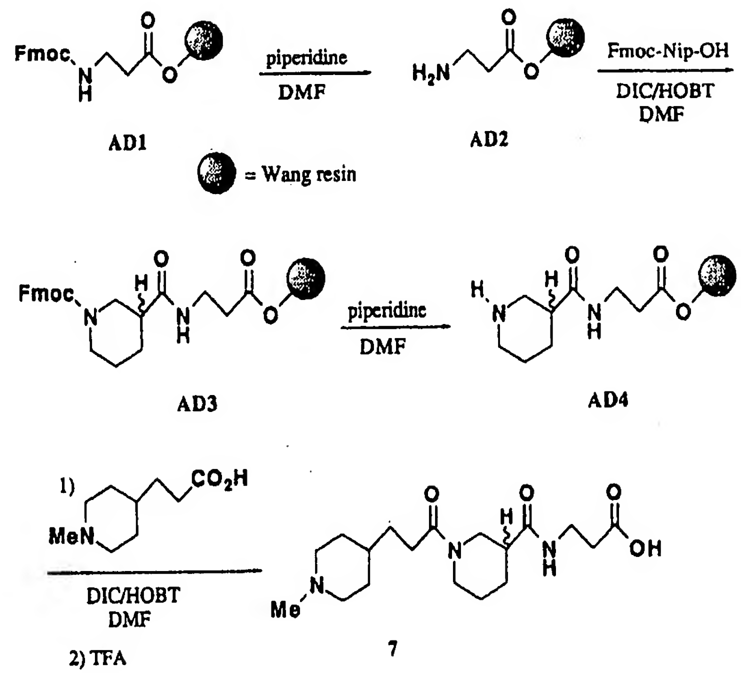
SCHEME AB



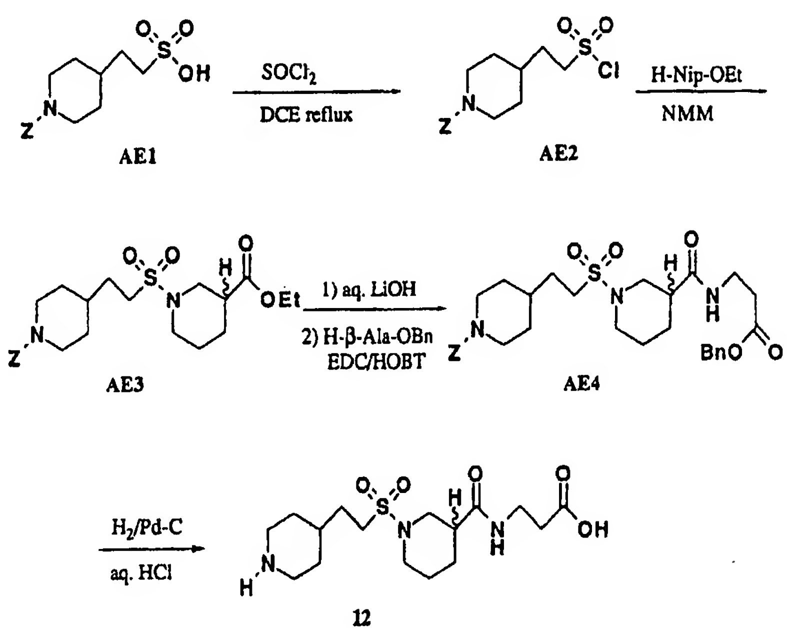
SCHEME AC



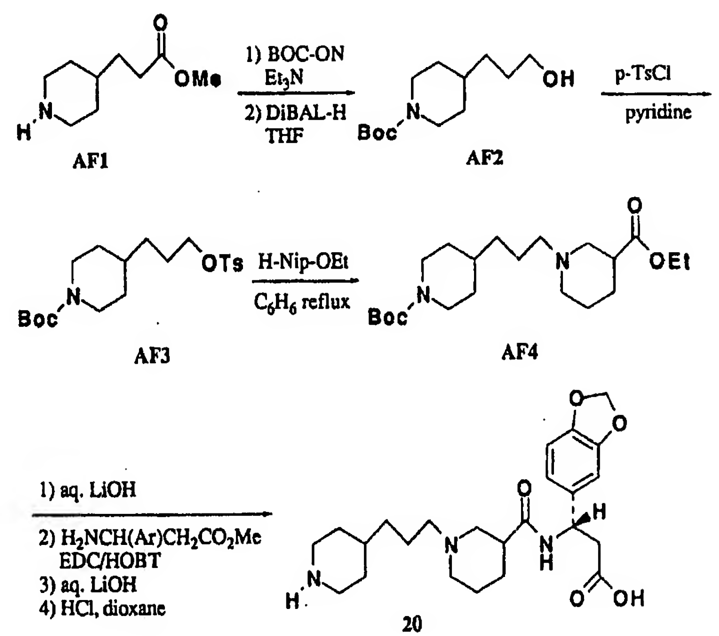
SCHEME AD



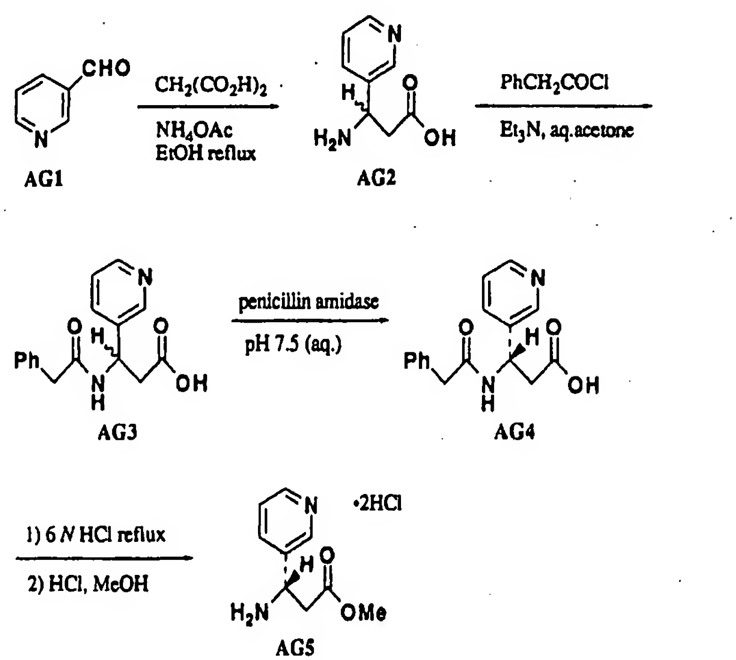
SCHEME AE



SCHEME AF

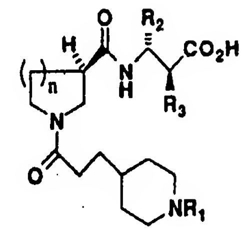


SCHEME AG

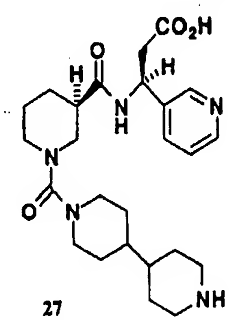


Particularly preferred compounds of the present invention include those compounds shown in Table 1 (and Table 2), where the letter "R" after the numeral "3" indicates the absolute configuration (Cahn-Ingold-Prelog rules).

TABLE II



#	n	R1	R2	R3
22	2	H	H	NHCONH(3-MeOPh)
23	2	H	H	$NHCOOCH_2Ph$
24	2	H	H	$NHCOOCH_2$(3-ClPh)
25	2	H	H	$NHSO_2CH_2Ph$
26	2	H	H	NHCONH(3,5-diMeOPh)
27	See structure below			
28	2	H	H	NHCONH(2-naphthyl)
29	See structure below			
30	2	H	H	$NHCONHCH_2CH_2Ph$
31	2	H	6-Me-3-pyridyl	H
32	2	H	5-Br-3-pyridyl	H
33	2	CH(NH)	3-pyridyl	H



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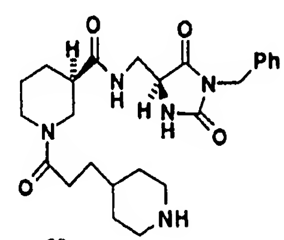
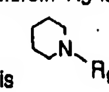
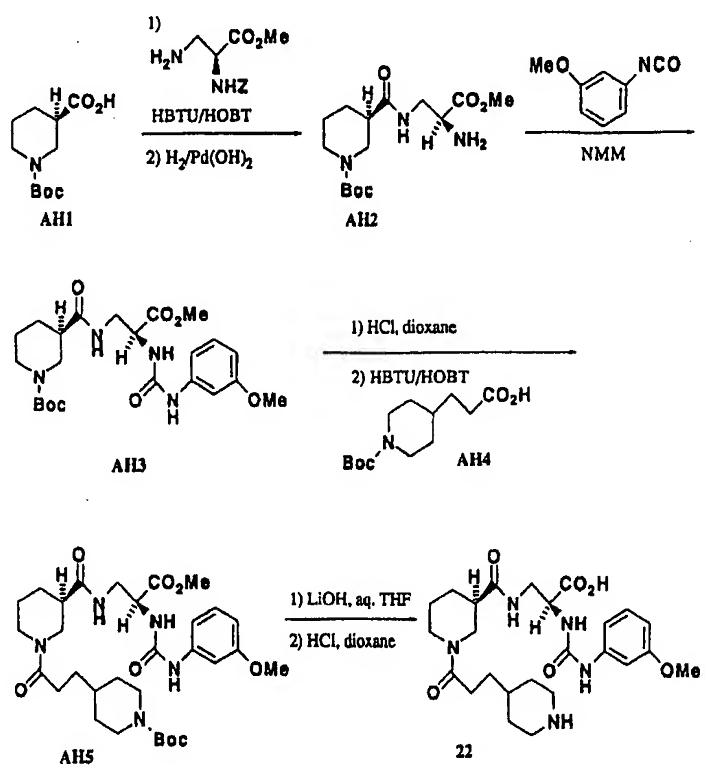


29

The diaminopropionic acid antagonists of the invention wherein R_5 is $C(O)NHQ(CHW)_rCO_2R_8$, R_{10} is H, M is piperidin-1-yl and A is 

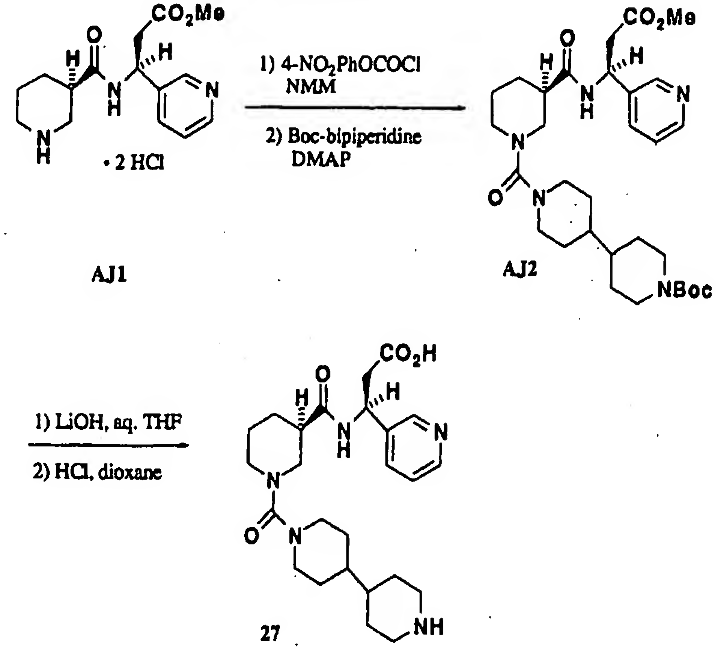
may be prepared as shown in Scheme AH. Methyl N-α-Z-diaminopropionate was acylated by HBTU-activated AH1, the Z group removed by hydrogenolysis to afford AH2 (for **23** the Z group was retained), and then the resultant primary amine reacted with the requisite isocyanate (or alkyl chloroformate for **24**, alkylsulfonyl chloride for **25**) to give AH3. The Boc group of intermediate AH3 was removed with HCl and the resultant secondary amine acylated with HBTU-activated AH4 to give AH5. This material was saponified with lithium hydroxide and the Boc group removed with HCl to give **22**.

SCHEME AH



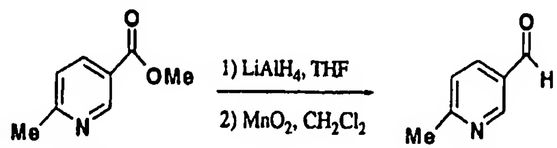
The bipiperidine-urea based antagonists of the invention may be prepared as shown in Scheme AJ. Intermediate AJ1 was prepared as described in Scheme AG. AJ1 was acylated with *p*-nitrophenyl chloroformate and then reacted with Boc-bipiperidine (for a synthesis, see W. Bondinell, patent application WO 94/14776). The ester AJ2 was saponified with lithium hydroxide and the Boc group removed with HCl to afford **27**. Substituted piperidine aldehyde intermediates such as AK2 were prepared by lithium aluminum hydride reduction of their corresponding nicotinic acid methyl esters (AK1) followed by oxidation with manganese dioxide (Scheme AK). The aldehydes were then converted to β-amino acids as shown in Scheme AG. Formamidine AL3 was prepared as shown in Scheme AL. Amine AL1 was acylated with ethyl formimidate as described by M. K. Scott (*J. Med. Chem.* **1983**, *26*, 534). The ester AL2 was saponified with 4 *N* HCl (RT, 20 h) to afford **33**. Three-substituted β-amino acid-type antagonists were synthesized as shown in Scheme AM. Resolved 6-methyl-pyridyl-β-amino ester was acylated with HBTU-activated AM1, and the coupled product treated with HCl to afford amine AM2. The amine was acylated with HBTU-activated AM4, the ester saponified, and the Boc group removed with HCl to afford **31**.

SCHEME AJ



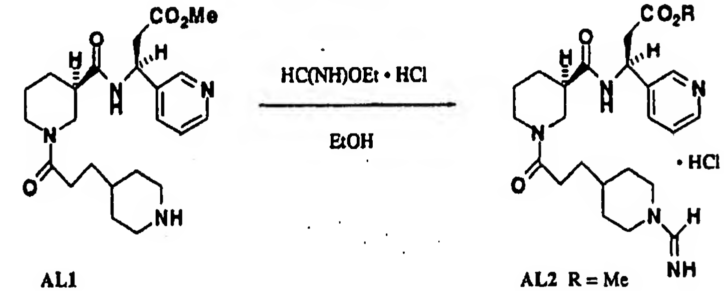
AJ1 AJ2 27

SCHEME AK



AK1 AK2

SCHEME AL

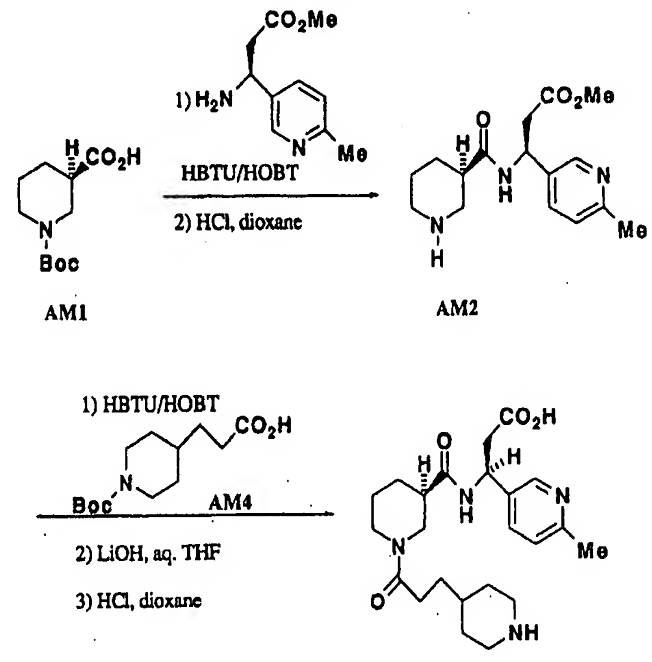


AL1

AL2 R = Me

33 R = H

SCHEME AM



AM1 AM2 31

To prepare the pharmaceutical compositions of this invention, one or more compounds of formula (I) or salt thereof of the invention as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 0.03 mg to 100 mg/kg (preferred 0.1-30 mg/kg) and may be given at a dosage of from about 0.1-300 mg/kg/day (preferred 1-50 mg/kg/day). The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

BIOLOGY

The compounds of the present invention interrupt binding of fibrinogen to platelet glycoprotein IIb/IIIa (GPIIb/IIIa) and thereby inhibit platelet

aggregation. Such compounds are, therefore, useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and angioplasty, and a variety of vasŏ-occlusive disorders. Because the final, common pathway in normal platelet aggregation is the binding of fibrinogen to activated, exposed GPIIb/IIIa, inhibition of this binding represents a plausible antithrombotic approach. The receptor is activated by stimuli such as ADP, collagen, and thrombin, exposing binding domains to two different peptide regions of fibrinogen: α-chain Arg-Gly-Asp (RGD) and γ-chain 400-411. As demonstrated by the results of the pharmacological studies described hereinafter, the compounds of the present invention show the ability to block fibrinogen binding to isolated GPIIb/IIa (IC_{50}'s 0.0002-1.39 μM), inhibit platelet aggregation *in vitro* in the presence of a various of platelet stimuli (0.019-65.0 μM vs. thrombin), and furthermore, inhibit *ex vivo* platelet aggregation in animal models.

IN VITRO SOLID PHASE PURIFIED GLYCOPROTEIN IIB/IIIA BINDING ASSAY.

A 96 well Immulon-2 microtiter plate (Dynatech-Immulon) is coated with 50 μl/well of RGD-affinity purified GPIIb/IIIa (effective range 0.5-10 μg/mL) in 10 mM HEPES, 150 mM NaCl, 1 mM at pH 7.4. The plate is covered and incubated overnight at 4°C. The GPIIb/IIa solution is discarded and 150 μl of 5% BSA is added and incubated at RT for 1-3 h. The plate is washed extensively with modified Tyrodes buffer. Biotinylated fibrinogen (25 μl/well) at 2 x final concentration is added to the wells that contain the test compounds (25 μl/well). The plate is covered and incubated at RT for 2-4 h. Twenty minutes prior to incubation completion, one drop of Reagent A (Vecta Stain ABC Horse Radish Peroxidase kit, Vector Laboratories, Inc.) and one drop Reagent B are added with mixing to 5 mL modified Tyrodes buffer mix and let stand. The ligand solution is discarded and the plate washed (5 x 200 μl/well) with modified Tyrodes buffer. Vecta Stain HRP-Biotin-Avidin reagent (50 μl/well, as prepared above) is added and incubated at RT for 15 min. The Vecta Stain solution is discarded and the wells washed (5 x 200 μl/well) with modified Tyrodes buffer. Developing buffer (10 mL of 50 mM citrate/phosphate buffer @ pH 5.3, 6 mg o-phenylenediamine, 6 μl 30% H_2O_2; 50 μl/well) is added and incubated at

RT for 3-5 min, and then 2*N* H_2SO_4 (50 µl/well) is added. The absorbance is read at 490 nM. The results are shown in Tables III and IV.

IN VITRO INHIBITION OF THROMBIN-INDUCED GEL-FILTERED PLATELET AGGREGATION ASSAY.

The percentage of platelet aggregation is calculated as an increase in light transmission of compound-treated platelet concentrate vs. control-treated platelet concentrate. Human blood is obtained from drug free, normal donors into tubes containing 0.13*M* sodium citrate. Platelet rich plasma (PRP) is collected by centrifugation of whole blood at 200 x g for 10 min at 25°C. The PRP (5 mL) is gel filtered through Sepharose 2B (bed volume 50 mL), and the platelet count is adjusted to $2x10^7$ platelets per sample. The following constituents are added to a siliconized cuvette: concentrated platelet filtrate and Tyrode's buffer (0.14*M* NaCl, 0.0027*M* KCl, 0.012*M* $NaHCO_3$, 0.76 *mM* Na_2HPO4, 0.0055*M* glucose, 2 mg/mL BSA and 5.0*mM* HEPES @ pH 7.4) in an amount equal to 350 µl, 50 µl of 20 *mM* calcium and 50 µl of the test compound. Aggregation is monitored in a BIODATA aggregometer for the 3 min following the addition of agonist (thrombin 50 µl of 1 unit/mL). The results are shown in Tables III and IV.

TABLE III

In Vitro Results

Compound #	Fibrinogen Binding % Inh. (50 µM)	Fibrinogen Binding IC_{50} (µM)	Platelet Aggregation* % Inh. (50µM)	Platelet Aggregation* IC_{50} (µM)
1	95.0%	0.003	83.0%	3.6
2	93.0%	0.027	95.7%	54.0
3	81.0%	NT	26.2%	>100
4	89.9%	0.121	81.0%	26.0
5	89.0%	0.012	100%	10.0
6	90.7	0.197	71.2%	73.0
7	100%	0.006	75.6%	2.4
8	93.0%	0.332	94.8%	65.0
9	99.0%	0.002	90.9%	0.37
10	91.3%	0.019	85.0%	1.6
11	79.6%	0.004	99.2%	1.55
12	97.0%	0.025	88.0%	15.5
13	95.0%	1.39	67.0%	25.5
14	99.0%	0.004	91.0%	0.91
15	100%	0.0091	92.2%	1.9
16	100%	0.0005	94.0%	0.028
17	96.0%	0.005	89.6%	0.45
18	100%	0.0002	100%	0.019
19	99.0%	0.021	92.1%	0.079
20	99.0%	0.0007	89.7%	37.0
21	100%	0.0005	100%	0.060

* Thrombin-induced aggregation of gel-filtered platelets.

TABLE IV
In Vitro Results

Compound #	Fibrinogen Binding % Inh. (50 uM)	Fibrinogen Binding IC_{50} (uM)	Platelet Aggregation* % Inh. (50uM)	Platelet Aggregation* IC_{50} (uM)
22	100%	0.0007	94.0%	0.046
23	100%	0.0003	97.0%	0.027
24	100%	0.0004	100%	0.018
25	100%	0.0003	97.0%	0.007
26	100%	0.0003	97.0%	0.016
27	100%	0.0006	100%	0.45
28	100%	0.0002	100%	0.17
29	100%	0.068	100%	42
30	100%	0.0008	100%	0.19
31	100%	0.0003	100%	0.045
32	100%	0.0004	100%	0.020
33	100%	0.0007	100%	0.30

* Thrombin-induced aggregation of gel-filtered platelets.

EX VIVO DOG STUDY

Adult mongrel dogs (8-13 kg) were anesthetized with sodium pentobarbital (35 mg/kg, i.v.) and artificially respired. Arterial blood pressure and heart rate were measured using a Millar catheter-tip pressure transducer inserted in a femoral artery. Another Millar transducer was placed in the left ventricle (LV) via a carotid artery to measure LV end diastolic pressure and indices of myocardial contractility. A lead II electrocardiogram was recorded from limb electrodes. Catheters were placed in a femoral artery and vein to sample blood and infuse drugs, respectively. Responses were continuously monitored using a Modular Instruments data aquisition system.

Arterial blood samples (5-9 ml) were withdrawn into tubes containing 3.8% sodium citrate to prepare platelet rich plasma (PRP) and to determine effects on coagulation parameters: prothrombin time (PT) and activated partial thromboplastin time (APTT). Separate blood samples (1.5 ml) were withdrawn in EDTA to determine hematocrit and cell counts (platelets, RBC's and white cells). Template bleeding times were obtained from the buccal surface using a symplate incision devise and Whatman filter paper.

Aggregation of PRP was performed using a BioData aggregometer. Aggregation of whole blood used a Chronolog impedance aggregometer. PT and APTT were determined on either a BioData or ACL 3000+ coagulation analyser. Cells were counted with a Sysmex K-1000.

Compounds were solubilized in a small volume of dimethylformamide (DMF) and diluted with saline to a final concentration of 10% DMF. Compounds were administered by the intravenous route with a Harvard infusion pump. Doses was administered over a 15 min interval at a constant rate of 0.33 ml/min. Data were obtained after each dose and in 30 min intervals following the end of drug administration. Oral doses were administered as aqueous solutions via syringe.

Compounds caused marked inhibition of ex vivo platelet aggregation responses. Thus, in whole blood, the compounds inhibited collagen-stimulated (or ADP) aggregation in doses of 0.1-10 mg/kg with marked inhibition of collagen stimulated platelet ATP release. In PRP, the compounds also inhibited collagen stimulated platelet aggregaton with marked activity at 0.1-10 mg/kg. Compounds had no measurable hemodynamic effect in doses up to 1 mg/kg, iv. The drugs produce an increase in template bleeding time at 0.1-1 mg/kg with rapid recovery post treatment. No effects on coagulation (PT or APTT) were observed during treatment and platelet, white and RBC counts were unchanged at any dose of the compounds.

The results indicate that the compounds are broadly effective inhibitors of platelet aggregation ex vivo (antagonizing both collagen and ADP pathways) following iv administration of doses ranging from 0.1-1 mg/kg or 1-10 mg/kg orally (Tables V and VI). The antiaggregatory effects are accompanied by increases in bleeding time at the higher doses. No other hemodynamic or hematologic effects are observed.

TABLE V
Ex Vivo Dog Study Results

Compound #	Intravenous Dosing Dose	Intravenous Dosing Duration*	Oral Dosing Dose	Oral Dosing Duration*
15	1 mpk	30 min	10 mpk	120 min
16	0.1 mpk	60 min	1 mpk	60 min

	0.3 mpk	NT	3 mpk	>180 min
18	0.1 mpk	30 min	1 mpk	150 min
19	1 mpk	30 min	10 mpk	90 min
21	0.3 mpk	150 min	1 mpk	180 min

* Indicates duration of >50% inhibition of collagen- or ADP-induced ex vivo platelet aggregation.

TABLE VI

Ex Vivo Dog Study Results

	Intravenous Dosing		Oral Dosing	
Cmpd #	Dose	Duration*	Dose	Duration*
22	0.3 mpk	180 min	3 mpk	60 min
23	0.1 mpk	60 min	1 mpk	180 min
	0.3 mpk	NT	3 mpk	150 min
24	0.3 mpk	90 min	3 mpk	120 min
25	0.3 mpk	30 min	3 mpk	60 min
26	0.3 mpk	NT	3 mpk	60 min
27	0.3 mpk	60 min	3 mpk	120 min
28	0.3 mpk	NT	3 mpk	120 min
30	0.3 mpk	105 min	3 mpk	180 min
31	0.3 mpk	120 min	3 mpk	>180 min
31	0.3 mpk	60 min	3 mpk	180 min

* Indicates duration of >50% inhibition of collagen-induced ex vivo platelet aggregation.

Compounds **16** and **18** have shown efficacy in a canine arteriovenous shunt model of thrombosis in a dose-dependent fashion (method in "Nipecotic Acid Derivatives As Antithrombotic Compounds," application Serial No. 08/213772, filed March 16, 1994). For instance, compound **16** inhibits thrombus formation at 10, 30, and 100 µg/kg/min cumulative doses by iv infusion (75%, 37%, 12% of thrombus weight vs. vehicle control, respectively). Compound **18** inhibits thrombus formation at 3, 10, and 30 µg/kg/min cumulative doses by iv infusion (82%, 41%, 12% of thrombus weight vs. vehicle control, respectively).

EXAMPLES

Protected amino acids were purchased from Aldrich Chemical or Bachem Bioscience Inc. 2-Chlorotrityl resin and Wang resin were obtained from Novabiochem Corp. Enantiomerically-enriched cycloalkylidene-3-carboxylic acid ethyl esters were isolated by chiral resolution of racemic material as published (A. M. Akkerman, *Rec. Trav. Chim. Pays-Bas* **1951**, *70*, 899). All other chemicals were purchased from Aldrich Chemical Company, Inc. Final product acid addition salts can be converted to free bases by basic ion exchange chromatography. High field ^{1}H NMR spectra were recorded on a Bruker AC-360 spectrometer at 360 MHz, and coupling constants are given in Herz. Melting points were determined on a Mel-Temp II melting point apparatus and are uncorrected. Microanalyses were performed at Robertson Microlit Laboratories, Inc., Madison, New Jersey. In those cases where the product is obtained as a salt, the free base is obtained by methods known to those skilled in the art, *e.g.* by basic ion exchange purification. In the Examples and throughout this application, the following abbreviations have the meanings recited hereinafter.

Bn or Bzl = Benzyl
Boc = t-Butoxycarbonyl
BOC-ON = 2-(*t*-Butoxycarbonyloxyimino)-2-phenylacetonitrile
BOP-Cl = Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
CP = compound
DCE = 1,2-Dichloroethane
DCM = Dichloromethane
DIBAL-H = Diisobutylaluminum hydride
DIC = Diisopropylcarbodiimide
DIEA = Diisopropylethylamine
DMAP = 4-Dimethylaminopyridine
DMF = N, N-Dimethylformamide
EDC = Ethyl dimethylaminopropylcarbodiimide
EDTA = Ethylenediaminetetraacetic acid
Et_2O = Diethyl ether
HBTU = 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBT = Hydroxybenzotriazole
i-Pr = Isopropyl

KOTMS = Potassium trimethylsilanolate
NMM = N-Methylmorpholine
Nip = Nipecotyl (unless noted otherwise, racemic at 3-position)
NT = not tested
PPT = precipitate
PTSA = *p*-Toluenesulfonic acid
RT = room temperature
TFA = Trifluoroacetic acid
$TMSN_3$ = Azidotrimethylsilane
Z = Benzyloxycarbonyl

Allyl 3-(4-piperidine)propionate • HCl (AA1 precursor)

To a mixture of 3-(4-pyridine)acrylic acid (10.0 g, 0.066 mol) and aqueous HCl (2.0 *N*, 50 mL) under a blanket of nitrogen was added platinum (IV) oxide (0.54 g). This mixture was hydrogenated at 50 psi and RT for 21 h, filtered through Celite, and evaporated to give 3-(4-piperidine)propionic acid • HCl as a white powder (12.9 g, 99%). This powder was treated with allyl alcohol (50 mL) and warmed at 50°C for 2 h. This solution was cooled to RT, evaporated to *ca.* 10 mL volume, and diluted with Et_2O (250 mL). The resultant precipitate was collected and washed with Et_2O to afford a white powder (14.5 g, 94%): ^1H NMR (DMSO-d_6) δ 8.7-9.1 (m, 2 H), 5.9 (m, 1 H), 5.25 (dd, J=7, 15, 2 H), 4.53 (d, J=4, 2 H), 3.21 (d, J=8, 2 H), 2.74 (t, J=7, 2 H), 2.35 (t, J=4, 2 H), 1.72 (d, J=8, 2 H), 1.5 (m, 3 H), 1.3 (m, 2 H); MS m/e 198 (MH^+).

Methyl (S)-3-amino-3-(3-pyridyl) propionate • 2HCl (AG5)

Phenylacetamide intermediate AG3 was prepared using standard methods as shown in Scheme AG (E. Profft, *J. Prakt. Chem.* 1965, *30*, 18). A mixture of AG1 (0.47 mol), EtOH (100 mL), NH_4OAc (0.47 mol), and malonic acid (0.70 mol) was heated at reflux for 6 h, cooled, and filtered. The white solid was washed with EtOH and MeOH and dried. This solid was dissolved in 2:1 acetone/water (360 mL), treated with triethylamine (0.72 mol) and phenylacetyl chloride (0.36 mol), and stirred for 22 h. The mixture was evaporated and the residue dissolved in water (500 mL) and adjusted to pH

12 (1 *N* NaOH). The aqueous layer was adjusted to pH 2 (conc. HCl), extracted with Et_2O, and evaporated to a white foam. The foam was purified by silica gel chromatography (10% MeOH/DCM) to give AG3. A solution of compound AG3 (0.22 mol) in water (600 mL) at RT was adjusted to pH 7.5 using KOH (3.0 *N*) and treated with penicillin amidase (91520 units, Sigma). This mixture was stirred for 47 h, acidified to pH 1 with HCl (conc), and the resultant ppt filtered through Celite. The filtrate was extracted with Et_2O (3x300 mL), concentrated *in vacuo*, and treated with MeOH/conc. NH_4OH (9:1). This product-containing solution was purified by silica gel chromatography (eluent DCM/MeOH/NH_4OH, 78:18:4) to give (S)-3-phenylacetamido-3-(3-pyridyl) propionic acid ammonium salt (19.5 g, 58%). This product was treated with HCl (6.0 N, 292 mL), heated at reflux for 5 h, cooled to RT, and extracted with Et_2O (3x200 mL). The aqueous layer was adjusted to pH 12, concentrated *in vacuo*, and the resultant solid triturated with MeOH (2x300 mL). This solution was evaporated to give *ca.* 14 g sodium salt. This material was treated with MeOH (500 mL), 2,2-dimethoxypropane (44 mL), and HCl (4 *N* in dioxane, 84 mL), and stirred for 90 h at RT. This mixture was filtered and the filtrate concentrated *in vacuo*. The resultant off-white solid was triturated with Et_2O (2 x 150 mL) and dried to give compound AG5 (16.7 g, 96% ee) as a white, amorphous solid.

EXAMPLE 1

N-3-(4-Piperidinepropionyl)-nipecotyl-(3-amino-3-phenyl) propionic acid • TFA (1)

A 25 mL sintered glass vessel under nitrogen was charged with 2-chlorotrityl chloride resin (0.24 g, 0.36 mmol, Novabiochem) and DMF (5 mL). The resin was agitated with nitrogen for 5 min to swell and the DMF removed. The resin was treated with DMF (5 mL), DIEA (0.31 mL, 5 eq), and allyl 3-(4-piperidine)propionate • HCl (0.20 g, 2.4 eq), sequentially, and agitated for 8 h. The resultant dark green solution was removed, and the resin washed with DMF (3x5 mL), aqueous DMF (25%, 3x5 mL), THF (3x5 mL), DCM (3x5 mL), and Et_2O (5 mL). The resin was swelled with DCE (5 mL) and treated with a mixture of tetrabutylammonium fluoride hydrate (0.28 g, 3 eq), azidotrimethylsilane (0.38 mL, 10 eq), tetrakis(triphenylphosphine)palladium (0.084 g, 20 mol %), and DCE (5 mL). The resin was agitated for 15 h and

the orange solution removed. The resin was washed with DCM (3x5 mL), DMF (3x5 mL), THF (3x5 mL), and Et_2O (5 mL). The resin was swelled with DMF (5 mL) and treated with DIEA (0.18 mL, 3 eq), allyl nipecotate • HCl (0.17 g, 3 eq), DIC (0.17 mL, 3 eq), and HOBT (1 mg). The resin was agitated for 15 h and then the reaction solution removed. The resin was washed with DMF (3x5 mL), aqueous DMF (25%, 3x5 mL), THF (3x5 mL), DCM (3x5 mL), and Et_2O (5 mL). The resin was swelled with DCE (5 mL) and treated with a mixture of tetrabutylammonium fluoride hydrate (0.28 g, 3 eq), azidotrimethylsilane (0.38 mL, 10 eq), tetrakis(triphenylphosphine) palladium (0.084 g, 20 mol %), and DCE (5 mL). The resin was agitated for 15 h and the orange solution removed. The resin was washed with DCM (3x5 mL), DMF (3x5 mL), THF (3x5 mL), and Et_2O (5 mL). The resin was swelled with DMF (5 mL) and treated with DIEA (0.18 mL, 3 eq), methyl D,L-3-amino-3-phenylpropionate • HCl (0.23 g, 3 eq), DIC (0.17 mL, 3 eq), and HOBT (1 mg). The resin was agitated for 17 h and then the reaction solution removed. The resin was washed with DMF (3x5 mL), aqueous DMF (25%, 3x5 mL), THF (3x5 mL), DCM (3x5 mL), and Et_2O (5 mL). The resin was swelled with THF (5 mL) and treated with a solution of KOTMS (0.23 g, 10 eq) and THF (2 mL). The resin was agitated for 18 h and then the reaction solution removed. The resin was washed with DMF (3x5 mL), acetic acid/THF (1:1, twice), aqueous DMF (25%, 3x5 mL), THF (3x5 mL), DCM (3x5 mL), and Et_2O (5 mL). The resin was treated with TFA/DCM (1:1, 10 mL), agitated for 15 min, and the resultant red solution collected. This solution was evaporated and the resultant oil triturated with Et_2O (3x5 mL) and dried to afford compound 1 as a clear glass (0.11 g): ^1H NMR (DMSO-d_6) δ 8.6 (m, 1 H), 8.42 (d, J=7, 1 H), 8.2 (m, 1 H), 7.3 (m, 3 H), 7.2 (m, 2 H), 5.18 (d, J=6, 1 H), 4.3 (m, 1 H), 3.7 (m, 1 H), 3.2 (m, 3 H), 2.8 (m, 2 H), 2.6 (m, 2 H), 2.3 (m, 5 H), 1.1-1.9 (m, 11 H); MS m/e 416 (MH^+).

• • •

Using the same general solid phase synthesis technique as described in Example 1, the compounds of indicated examples were made according to Scheme AA as recited in the particular example.

EXAMPLE 2

N-(4-Piperidinemethylaminocarbonyl)-nipecotyl-(3-amino-2-methyl) propionic acid • TFA (2)

Compound **2** was prepared as shown in Scheme AA. Resin-bound 4-piperidinemethylamine (0.36 mmol) was swelled with DCE (5 mL), treated with *p*-nitrophenylchloroformate (0.36 mmol) and DIEA (0.36 mmol), agitated for 1 h, and the solvent removed. The resin was washed (see Example 1), swelled with DCE (5 mL), treated with allyl nipecotate • HCl (0.36 mmol) and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the allyl ester cleaved to the corresponding acid (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with methyl 3-amino-2-methylpropionate (0.36 mmol), and the synthesis completed as shown in Example 1. Compound **2** was isolated as a clear glass (0.11 g): ^1H NMR (CD_3OD) δ 3.9 (m, 2 H), 3.2 (m, 4 H), 3.10 (d, J=7, 2 H), 2.9 (m, 3 H), 2.6 (m, 2 H), 2.3 (m, 1 H), 1.9 (m, 4 H), 1.7-1.9 (m, 5 H), 1.3-1.5 (m, 5 H), 1.11 (d, J=7, 3 H); MS m/e 355 (MH^+).

EXAMPLE 3

N-(4-Piperidinemethyloxycarbonyl)-nipecotyl-D-aspartic acid α-methyl ester • TFA (3)

Compound **3** was prepared as shown in Scheme AA. Resin-bound 4-piperidinemethanol (0.36 mmol) was swelled with DCE (5 mL), treated with *p*-nitrophenylchloroformate (0.36 mmol) and DIEA (0.36 mmol), agitated for 1 h, and the solvent removed. The resin was washed (see Example 1), swelled with DCE (5 mL), treated with allyl nipecotate • HCl (0.36 mmol) and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the allyl ester cleaved to the corresponding acid (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with H-D-Asp(OBn)-OMe (0.36 mmol), and the synthesis completed as shown in Example 1. Compound **3** was isolated as a yellow glass (0.019 g): ^1H NMR (CD_3OD) δ 4.8 (m, 2 H), 3.9 (m, 3 H), 3.70 (d, J=9, 4 H), 3.39 (s, 3 H), 3.3 (m, 2 H), 2.9 (m, 4 H), 2.8 (m, 2 H), 1.9 (m, 4 H), 1.7 (m, 2 H), 1.4 (m, 4 H); MS m/e 400 (MH^+).

EXAMPLE 4

N-3-(4-Piperidinepropionyl)-pyrrolidine-3-carboxy-[3-amino-3-(4-tolyl)] propionic acid • TFA (4)

Compound **3** was prepared as shown in Scheme AA. Intermediate AA2 (0.36 mmol) was swelled with DCE (5 mL), treated with methyl pyrrolidine-3-carboxylate • HCl (0.36 mmol), DIC (0.72 mmol), and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the methyl ester cleaved to the corresponding acid with KOTMS (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with methyl 3-amino-3-(4-tolyl)propionate (0.36 mmol), and then the synthesis completed as shown in Example 1. Compound **4** was isolated as a clear glass (0.081 g): ^{1}H NMR (CD_3OD) δ 7.19 (d, J=5, 2 H), 7.10 (d, J=5, 2 H), 5.31 (dd, J=3, 10; 1 H) 3.6 (m, 4 H), 3.3 (m, 2 H), 2.9 (m, 4 H), 2.7 (m, 2 H), 2.3 (m, 2 H), 2.1 (m, 3 H), 1.9 (m, 4 H), 1.6 (m, 4 H), 1.3 (m, 4 H); MS m/e 416 (MH+).

EXAMPLE 5

N-3-(4-Piperidinepropionyl)-isonipecotyl-(3-amino-3-methyl) propionic acid • TFA (5)

Compound **5** was prepared as shown in Scheme AA. Intermediate AA2 (0.36 mmol) was swelled with DCE (5 mL), treated with ethyl isonipecotate (0.36 mmol), DIC (0.72 mmol), and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the ethyl ester cleaved to the corresponding acid with KOTMS (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with methyl 3-amino-3-methylpropionate (0.36 mmol), and then the synthesis completed as shown in Example 1. Compound **5** was isolated as a tan glass (0.033 g): ^{1}H NMR (CD_3OD) δ 4.5 (m, 1 H), 4.2 (m, 1 H), 3.9 (m, 1 H), 3.3 (m, 2 H), 3.3 (m, 3 H), 3.1 (m, 1 H), 2.9 (m, 3 H), 2.7 (m, 2 H), 2.4 (m, 2 H), 2.0 (m, 2 H), 1.7 (m, 2 H), 1.5 (m, 6 H), 1.3 (m, 2 H), 1.15 (d, J=9, 3 H); MS m/e 354 (MH+).

EXAMPLE 6

N-3-(4-Piperidinepropionyl)-isonipecotyl-[3-amino-3-(4-carboxyphenyl)] propionic acid • TFA (6)

Compound **6** was prepared as shown in Scheme AA. Intermediate AA2 (0.36 mmol) was swelled with DCE (5 mL), treated with ethyl isonipecotate (0.36 mmol), DIC (0.72 mmol), and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the ethyl ester cleaved to the corresponding acid with KOTMS (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with methyl 3-amino-3-(4-carboxymethyl-phenyl)propionate (0.36 mmol), and then the synthesis completed as shown in Example 1. Compound **6** was isolated as a tan glass (0.034 g): ^{1}H NMR (CD_3OD) δ 7.9 (m, 3 H), 7.43 (d, J=5, 2 H), 5.4 (m, 1 H), 4.5 (m, 1 H), 4.0 (m, 1 H), 3.3 (m, 4 H), 3.1 (m, 1 H), 2.9 (m, 2 H), 2.7 (m, 2 H), 2.7 (m, 1 H), 2.5 (m, 4 H), 2.0 (m, 2 H), 1.2-1.9 (m, 10 H); MS m/e 460 (MH+).

EXAMPLE 7

N-3-(4-N-Methyl-piperidinepropionyl)-nipecotyl-3-aminopropionic acid • TFA (7)

Compound **7** was prepared as shown in Scheme AD. Resin-bound Fmoc-β-Ala (1 mmol) was treated with 20% piperidine/DMF (10 mL), agitated for 2h, and the solvent removed. The resin was washed with DMF, swelled with DMF (10 mL), and treated with Fmoc-nipecotic acid (1 mmol), DIC (2 mmol), and DIEA (1 mmol). The resin was agitated for 16 h, the solvent removed, and the resin washed with DMF and DCM. The resin was treated with 20% piperidine/DMF (10 mL) for 2h, the solvent removed, and the resin washed with DMF. The resin was swelled with DMF (10 mL), treated with 4-N-methylpiperidinepropionic acid (1 mmol), DIC (2 mmol), and DIEA (1 mmol), and agitated for 16 h. The solvent was removed and the resin washed with DMF and DCM. The resin was cleaved with 95% TFA (10 mL) and the TFA evaporated to afford **7** as a white powder (0.26 g): mp 172-177°C; ^{1}H NMR ($CDCl_3$) δ 4.4 (m, 1 H), 3.7 (m, 1 H), 3.4 (m, 1 H), 3.2 (m, 1 H), 3.1 (m, 1 H),

2.7 (m, 2 H), 2.3 (m, 6 H), 2.21 (s, 3 H), 1.9 (m, 4 H), 1.3-1.8 (m, 10 H); MS m/e 354 (MH+).

EXAMPLE 8

N-3-(4-Piperidinepropionyl)-nipecotyl-4-oxonipecotic acid • TFA (8)

Compound **8** was prepared as shown in Scheme AA. Intermediate AA2 (0.36 mmol) was swelled with DCE (5 mL), treated with ethyl nipecotate (0.36 mmol), DIC (0.72 mmol), and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the ethyl ester cleaved to the corresponding acid with KOTMS (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with methyl 4-oxo-nipecotate (0.36 mmol), and then the synthesis completed as shown in Example 1. Compound **8** was isolated as a clear glass (0.04 g): ^{1}H NMR (DMSO-d_6) δ 8.5 (m, 1 H), 8.2 (m, 1 H), 6.5 (m, 1 H), 4.3 (m, 1 H), 3.4-3.8 (m, 4 H), 3.2 (m, 2 H), 3.0 (m, 1 H), 2.8 (m, 2 H), 2.2-2.6 (m, 6 H), 1.8 (m, 2 H), 1.1-1.7 (m, 11 H); MS m/e 394 (MH+).

EXAMPLE 9

N-3-(4-Piperidinepropionyl)-nipecotyl-[3-amino-3-(2-trimethylsilylethynyl)] propionic acid • TFA (9)

Compound **9** was prepared as shown in Scheme AA. Intermediate AA2 (0.36 mmol) was swelled with DCE (5 mL), treated with ethyl nipecotate (0.36 mmol), DIC (0.72 mmol), and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the ethyl ester cleaved to the corresponding acid with KOTMS (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with methyl 3-amino-3-(2-trimethylsilylethynyl)propionate (for a preparation, see J. Zablocki, *J. Med. Chem.* **1995**, *38*, 2378; 0.36 mmol), and then the synthesis completed as shown in Example 1. Compound **9** was isolated as a yellow glass (0.12 g): ^{1}H NMR (CD_3OD) δ 3.8 (m, 1 H), 3.2-3.4 (m, 4 H), 2.9 (m, 3 H), 2.7 (m, 2 H), 2.3-2.5 (m, 2 H), 1.9 (m, 4 H), 1.1-1.9 (m, 13 H), 0.0 (s, 9 H); MS m/e 436 (MH+).

EXAMPLE 10

N-(6-Aminocaproyl)-nipecotyl-3-amino-3-(3-pyridyl)propionic acid • 3TFA (10)

Compound **10** was prepared as shown in Scheme AA. Resin-bound 6-aminocaproic acid (0.36 mmol) was swelled with DCE (5 mL), treated with ethyl nipecotate (0.36 mmol), DIC (0.72 mmol), and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the ethyl ester cleaved to the corresponding acid with KOTMS (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with methyl 3-amino-3-(3-pyridyl)propionate (0.36 mmol), and then the synthesis completed as shown in Example 1. Compound **10** was isolated as a clear glass (0.008 g): ^{1}H NMR (DMSO-d_6) δ 8.6 (m, 2 H), 8.1 (s, 1 H), 7.0-7.7 (m, 5 H), 5.15 (t, J=3, 1 H), 4.4 (m, 1 H), 4.1 (m, 1 H), 3.7 (m, 2 H), 3.1 (m, 1 H), 2.7 (m, 4 H), 2.5 (m, 1 H), 2.3 (m, 2 H), 1.2-1.9 (m, 11 H); MS m/e 391 (MH+). Anal. calcd. for $C_{20}H_{30}N_4O_4$ • 3TFA • $2H_2O$ (768.60): C, 40.63; H, 4.85; N, 7.29; F, 22.25. Found: C, 40.81; H, 4.70; N, 6.12; F, 23.83.

EXAMPLE 11

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-(3-amino-2-hydroxy) propionic acid • TFA (11)

Compound **11** was prepared as shown in Scheme AA. Intermediate AA2 (0.36 mmol) was swelled with DCE (5 mL), treated with ethyl R-nipecotate (0.36 mmol), DIC (0.72 mmol), and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the ethyl ester cleaved to the corresponding acid with KOTMS (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with methyl 3-amino-2-hydroxypropionate (0.36 mmol), and then the synthesis completed as shown in Example 1. Compound **11** was isolated as a pink glass (0.05 g): ^{1}H NMR (DMSO-d_6) δ 8.5 (m, 1 H), 8.2 (m, 1 H), 7.6 (m, 1 H), 4.0-4.4 (m, 2 H), 3.7 (m, 1 H), 3.2 (m, 3 H), 2.8 (m, 3 H), 2.6 (m, 1 H), 2.1-2.3 (m, 3 H), 1.8 (m, 4 H), 1.0-1.4 (m, 10 H); MS m/e 356 (MH+).

EXAMPLE 12

N-3-(4-Piperidineethanesulfonyl)-nipecotyl-3-aminopropionic acid • HCl (12)

Compound **12** was prepared as shown in Scheme AE. Intermediate AE1 was synthesized by the following procedure. 2-(4-Pyridine)ethanesulfonic acid (3.0 g, 0.016 mol) was dissolved in aq. HCl (2.0 N, 12 mL) and this solution treated with platinum dioxide (0.13 g) and hydrogenated at 50 psi and RT for 18 h. This mixture was filtered through Celite and evaporated to afford 2-(4-piperidine)ethanesulfonic acid • HCl (3.5 g, white powder). This powder was dissolved in aq. THF (1:1, 70 mL) at RT and treated with NMM (3.7 mL, 2.2 eq.) and benzyl chloroformate (2.2 mL, 1 eq.). This mixture was stirred for 15 h, acidified with aq. citric acid, and extracted with $CHCl_3$ (2x100 mL). The organic layer was dried with Na_2SO_4 and evaporated to afford 2-(4-N-Z-piperidine)ethanesulfonic acid (2.75 g, gold oil). This oil was converted to final product **12** in five synthetic steps (Scheme AE, W. J. Hoekstra, *J. Med. Chem.* **1995**, *38*, 1582) and isolated as a clear glass (0.060 g): ^{1}H NMR (DMSO-d_6) δ 8.9 (m, 1 H), 8.6 (m, 1 H), 3.5 (m, 2 H), 3.1-3.3 (m, 4 H), 3.0 (m, 2 H), 2.6-2.8 (m, 4 H), 2.3 (m, 3 H), 1.65-1.9 (m, 5 H), 1.6 (m, 3 H), 1.2-1.4 (m, 5 H); MS m/e 376 (MH+).

EXAMPLE 13

N-3-(4-Piperidinepropionyl)-nipecotyl-5H-(2-aminoethyl)tetrazole • HCl (13)

Compound **13** was prepared as shown in Scheme AC. Intermediate AC1 (prepared as in W. J. Hoekstra, *J. Med. Chem.* **1995**, *38*, 1582; 1.9 mmol) was dissolved in DCM (50 mL) and treated with BOP-Cl (1.9 mmol), NMM (1.9 mmol), and 3-aminopropionitrile (1.9 mmol). The reaction was stirred for 18 h, diluted with sat'd NH_4Cl, and the layers separated. The organic layer was evaporated and the product purified by silica gel chromatography (10%EtOH/DCM) to give an oil. The oil was dissolved in toluene (10 mL), treated with azidotrimethylsilane (2.4 mmol) and dibutyltin oxide (1.2 mmol), and heated at reflux for 16 h. Cooling gave a brown ppt which was triturated

with Et_2O. This solid was hydrogenated over platinum dioxide (0.08 g) in MeOH (12 mL) at 50 psi for 15 h, filtered, and evaporated to give **13** as a yellow foam (0.065 g): ^{1}H NMR (DMSO-d_6) δ 8.9 (m, 1 H), 8.6 (m, 1 H), 8.13 (d, J=28, 1 H), 4.2 (m, 2 H), 3.2 (m, 3 H), 3.0 (m, 4 H), 2.7 (m, 4 H), 2.31 (q, J=8, 2 H), 1.7-1.9 (m, 3 H), 1.4-1.6 (m, 5 H), 1.1-1.3 (m, 4 H); MS m/e 364 (MH+).

EXAMPLE 14

N-3-(4-N-Methyl-piperazinepropionyl)-nipecotyl-[3-amino-3-(3,4-methylenedioxyphenyl)]propionic acid • Na (14)

Compound **14** was prepared as shown in Scheme AB. Ethyl nipecotate (3 mmol) was dissolved in DCM (50 mL), treated with acryloyl chloride (3 mmol) and NMM (3 mmol), and stirred for 1 h. The solvent was evaporated and the residue dissolved in EtOH (50 mL) and treated with N-methylpiperazine (3 mmol). The solution was warmed at 60°C for 15 h, cooled to RT, and the solvent evaporated. The residue was partitioned between DCM (100 mL) and water (10 mL), and the layers separated. The organic layer was dried and evaporated to give a foam. The foam was dissolved in water, treated with NaOH (3 mmol), stirred for 1 h, and evaporated to give AB3•Na. The synthesis was completed as illustrated (W. J. Hoekstra, *J. Med. Chem.* **1995**, *38*, 1582) using methyl 3-amino-3-(3,4-methylenedioxyphenyl)propionate (2.5 mmol) to give **14** as a white, amorphous solid (0.14 g): ^{1}H NMR (D_2O) δ 6.8 (m, 3 H), 5.91 (s, 2 H), 5.0 (m, 1 H), 4.0 (m, 1 H), 3.7 (m, 1 H), 2.8-3.4 (m, 11 H), 2.69 (s, 3 H), 2.4-2.6 (m, 7 H), 1.9 (m, 1 H), 1.7 (m, 2 H), 1.5 (m, 1 H); MS m/e 475 (MH+). Anal. calcd. for $C_{24}H_{33}N_4O_6$ • Na • H_2O (514.56): C, 56.02; H, 6.86; N, 10.89. Found: C, 55.72; H, 6.78; N, 10.52.

EXAMPLE 15

N-3-(4-N-Methyl-piperazinepropionyl)-nipecotyl-[3-amino-3-(3-quinolinyl)]propionic acid • 3TFA (15)

Compound 15 was prepared as described in Example 14. The synthesis was completed as illustrated (W. J. Hoekstra, *J. Med. Chem.* 1995, *38*, 1582) using methyl 3-amino-3-(3-quinolinyl)propionate (6 mmol) with AB3. Compound 15 was isolated as a yellow powder (1.89 g): ^{1}H NMR (DMSO-d_6) δ 8.94 (s, 1 H), 8.12 (s, 1 H), 7.9 (m, 2 H), 7.6 (m, 2 H), 7.07 (d, J=4, 1 H), 5.2 (m, 1 H), 4.1 (m, 1 H), 3.7 (m, 1 H), 3.1-3.3 (m, 2 H), 2.9 (m, 2 H), 2.6 (m, 2 H), 2.43 (s, 3 H), 1.9-2.4 (m, 12 H), 1.2-1.5 (m, 4 H); MS m/e 482 (MH+).

EXAMPLE 16

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-[(S)-3-amino-3-(3,4-methylenedioxyphenyl)]propionic acid • HCl (16)

To a cooled (5°C) solution of Boc-R-nipecotic acid (9 mmol) and methyl (S)-3-amino-3-(3,4-methylenedioxyphenyl)]propionate (see AG5 example; 9 mmol) in MeCN (100 mL) was added HBTU (9 mmol), HOBT (9 mmol), and NMM (18 mmol). This mixture was stirred for 15 h, diluted with water (10 mL), and evaporated. The residue was diluted with EtOAc (100mL) and the organic layer dried and evaporated to give a white foam. The foam was treated with HCl (2 *N* in dioxane, 20 mL), stirred for 3 h, and evaporated to a foam. The foam was dissolved in MeCN (100 mL) and treated with Boc-piperidinepropionic acid (7 mmol), HBTU (7 mmol), HOBT (7 mmol), and NMM (14 mmol) with stirring for 6 h. The mixture was diluted with water (10 mL), evaporated, and diluted with EtOAc (100 mL). The organic layer was dried, evaporated, and purified by silica gel chromatography (7% EtOH/DCM) to give a foam. To a solution of the foam (4.6 mol) in THF cooled in an ice bath was added $LiOH \cdot H_2O$ (6.9 mmol dissolved in 30 mL water) dropwise. This mixture was stirred for 1.5 h, acidified with AcOH (1.7 mL), and warmed to RT. This solution was diluted with $CHCl_3$ (75 mL) and the layers separated. The organic layer was dried (Na_2SO_4) and evaporated to give a white foam. The foam was dissolved in dioxane (20 mL) and anisole

(0.3 mL), cooled in an ice bath, treated with HCl (15 mL, 4.0 *N* in dioxane), and stirred for 3 h to give a ppt. The ppt was filtered and washed with Et_2O (150 mL) and MeCN (20 mL) to give 16 as a white powder (1.78 g): mp 190-200°C; ^{1}H NMR (DMSO-d_6) δ 8.9 (m, 1 H), 8.6 (m, 1 H), 8.4 (m, 1 H), 6.83 (d, J=5, 1 H), 6.79 (d, J=5, 1 H), 6.7 (m, 1 H), 5.95 (s, 2 H), 5.08 (dd, J=5, 11, 1 H), 4.1-4.3 (m, 1 H), 3.7 (m, 1 H), 3.15 (d, J=10, 2 H), 3.0 (m, 1 H), 2.7 (m, 2 H), 2.6 (m, 3 H), 2.31 (d, J=7, 2 H), 1.81 (d, J=10, 2 H), 1.2-1.7 (m, 11 H); MS m/e 460 (MH+); $[\alpha]^{24}{}_D$ -0.478° (c 1.00, MeOH).

EXAMPLE 17

N-3-(4-Piperidinepropionyl)-hexahydroazepine-3-carboxy-[3-amino-3-(3-quinolinyl)]propionic acid • 2TFA (17)

Compound 17 was prepared as shown in Scheme AA. Intermediate AA2 (0.36 mmol) was swelled with DCE (5 mL), treated with methyl hexahydroazepine-3-carboxylate • HCl (0.36 mmol), DIC (0.72 mmol), and DIEA (0.72 mmoL), and agitated for 16 h. The solvent was removed, the resin washed (see Example 1), and the methyl ester cleaved to the corresponding acid with KOTMS (see Example 1). The resin was swelled with DMF (5 mL), the acid coupled with methyl 3-amino-3-(3-quinolinyl)propionate (0.36 mmol), and then the synthesis completed as shown in Example 1. Compound 17 was isolated as a glass (0.10 g): ^{1}H NMR (D_2O) δ 9.06 (s, 1 H), 8.9 (m, 1 H), 8.2 (m, 1 H), 8.04 (s, 1 H), 8.0 (t, J=4, 2 H), 7.8 (t, J=4, 2 H), 5.5 (m, 1 H), 3.8 (m, 1 H), 3.3 (m, 4 H), 3.0 (m, 2 H), 2.7 (m, 4 H), 2.0-2.4 (m, 6 H), 1.7-1.9 (m, 4 H), 1.1-1.6 (m, 8 H); MS m/e 481 (MH+).

EXAMPLE 18

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-[(S)-3-amino-3-(3-quinolinyl)]propionic acid • 2HCl (18)

Compound 18, prepared as described in Example 16 starting with Boc-R-nipecotic acid (7.1 mmol) and methyl (S)-3-amino-3-(3-quinolinyl)propionate (see example AG5; 7.1 mmol), was isolated as white flakes (1.11 g): mp 142-144°C; MS m/e 467 (MH+); $[\alpha]^{24}{}_D$ -173° (c 0.1, MeOH). Anal. calcd. for

$C_{26}H_{34}N_4O_4$ • 2.25 HCl • H_2O (566.64): C, 55.11; H, 6.80; N, 9.89; Cl, 14.08. Found: C, 54.85; H, 6.62; N, 10.04; Cl, 13.68.

EXAMPLE 19

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-[(S)-3-amino-3-(2-t-butylethynyl)] propionic acid • HCl (19)

Compound **19**, prepared as described in Example 16 starting with Boc-R-nipecotic acid (3.2 mmol) and methyl (S)-3-amino-3-(2-*t*-butylethynyl)propionate (see J. A. Zablocki, *J. Med. Chem.* **1995**, *38*, 2378; 3.2 mmol), was isolated as a white powder (0.33 g): MS m/e 420 (MH+). Anal. calcd. for $C_{23}H_{37}N_3O_4$ • 1.07 HCl • 0.43 H_2O (468.97): C, 59.21; H, 8.42; N, 8.96; Cl, 8.09. Found: C, 58.92; H, 8.58; N, 8.76; Cl, 7.82.

EXAMPLE 20

N-3-(4-Piperidinepropyl)-nipecotyl-[(S)-3-amino-3-(3,4-methylenedioxyphenyl)]propionic acid • 2TFA (20)

Compound **20** was prepared as shown in Scheme AF. Intermediate AF3 (2.8 mmol) was dissolved in benzene (50 mL), treated with ethyl nipecotate (2.8 mmol), and heated at reflux for 7 h. The reaction was cooled, partitioned between water (15 mL) and EtOAc (70 mL), and the layers separated. The organic layer was dried and evaporated to give AF4. AF4 was converted to **20** as previously described (W. J. Hoekstra, *J. Med. Chem.* **1995**, *38*, 1582) and isolated as a white powder (0.33 g): ^{1}H NMR (CD_3OD) δ 8.6-8.8 (m, 3 H), 6.7-6.9 (m, 3 H), 5.91 (s, 2 H), 5.1-5.2 (m, 1 H), 3.3-3.5 (m, 4 H), 2.8-3.1 (m, 6 H), 2.6-2.7 (m, 3 H), 1.5-2.0 (m, 11 H), 1.2-1.4 (m, 4 H); MS m/e 446 (MH+).

EXAMPLE 21

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-[(S)-3-amino-3-(3-pyridyl)] propionic acid • 2TFA (21)

Compound **21**, prepared as described in Example 16 starting with Boc-R-nipecotic acid (6.4 mmol) and methyl (S)-3-amino-3-(3-pyridyl)propionate (see example AG5; 6.4 mmol), was isolated as a white amorphous solid (1.60 g): mp 74-81°C; MS m/e 417 (MH+). Anal. calcd. for $C_{22}H_{32}N_4O_4$ • 2.1 $C_2HF_3O_2$ • 0.7 H_2O (668.58): C, 47.07; H, 5.35; N, 8.38; F, 17.90; KF, 1.89. Found: C, 47.08; H, 5.31; N, 8.41; F, 17.68; KF, 2.00.

EXAMPLE 22

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(3-methoxyanilino)carbonylamino-3-amino]propionic acid (22)

Methyl Boc-R-nipecotyl-[(S)-2-Z-amino-3-amino]propionate (prepared from methyl N-α-Z-L-diaminopropionate and Boc-R-nipecotic acid as shown in Example 16; 9.5 mmol) was dissolved in MeOH (40 mL) and hydrogenated at 50 psi over palladium hydroxide (0.4 g) for 24 h. The mixture was filtered and evaporated to give white solid AH2. AH2 (9.1 mmol) was dissolved in DCM (100 mL), cooled (5°C), treated with 3-methoxyphenylisocyanate (9.1 mmol) and NMM (9.1 mmol), and stirred for 17 h. The solution was diluted with sat'd NH_4Cl (10 mL), the layers separated, and the organic layer dried, evaporated to an oil, and purified by silica gel chromatography (4% EtOH/DCM) to give AH3. Intermediate AH3 was converted to **22** in four steps as in Example 16 to afford a white amorphous solid (1.35 g): mp 72-76°C; ^{1}H NMR (DMSO-d_6) δ 8.7 (m, 3 H), 7.8 (m, 1 H), 7.1 (m, 2 H), 6.8 (d, 1 H), 6.5 (d, 2 H), 3.66 (s, 3 H), 3.4 (m, 2 H), 3.2 (d, 2 H), 2.7 (dd, 4 H), 2.3 (m, 3 H), 1.6 (m, 3 H), 1.1-1.7 (m, 11 H); MS m/e 504 (MH+). Anal. calcd. for $C_{25}H_{37}N_5O_6$ • 1.2 HCl • 1.0 H_2O (565.37): C, 53.11; H, 7.17; N, 12.39; Cl, 7.53. Found: C, 53.40; H, 7.44; N, 12.14; Cl, 7.66.

Using the same general synthesis technique as described in Example **22**, the compounds of Examples **26**, **28-30** were made according to Scheme AH recited in the particular example. For carbamate analogues,

the acylating agent employed was the appropriate alkyl chloroformate (analogous conversion of AH2 to AH3; one molar equivalent). For sulfonamides, the sulfonating agent employed was the appropriate sulfonyl chloride (one molar equivalent).

EXAMPLE 23

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-benzyloxycarbonylamino-3-amino]propionic acid • HCl (23)

Compound **23**, prepared from methyl N-α-Z-L-diaminopropionate (8.8 mmol) and Boc-R-nipecotic acid (8.8 mmol) as shown in Example 16, was isolated as a white powder (1.65 g): mp 110-113°C; MS m/e 489 (MH+). Anal. calcd. for $C_{25}H_{36}N_4O_6$ • 1.15 HCl • 0.5 H_2O • 0.5 Dioxane (583.57): C, 55.56; H, 7.41; N, 9.60; Cl, 6.99. Found: C, 55.23; H, 7.79; N, 9.85; Cl, 7.01.

EXAMPLE 24

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(3-chlorobenzyloxy)carbonylamino-3-amino]propionic acid • HCl (24)

Compound **24**, prepared by reacting 3-chlorobenzyloxycarbonyl chloride (6.6 mmol) with AH2 (6.6 mmol) as described in Example 22, was isolated as a white amorphous solid (1.33 g): mp 89-96°C; MS m/e 524 (MH+). Anal. calcd. for $C_{25}H_{35}ClN_4O_6$ • 1.25 HCl • 0.5 H_2O • 1.0 Dioxane (637.20): C, 50.89; H, 7.08; N, 8.78; Cl, 12.52. Found: C, 51.10; H, 6.71; N, 8.38; Cl, 12.20.

EXAMPLE 25

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-benzylsulfonylamino-3-amino]propionic acid • HCl (25)

Compound **25**, prepared by reacting benzylsulfonyl chloride (5.2 mmol) with AH2 (5.2 mmol) as shown in Example 22, was isolated as a white powder

(0.87 g): mp 145-149°C; MS m/e 509 (MH+). Anal. calcd. for $C_{24}H_{36}N_4O_6S$ • 1.3 HCl • 0.3 Dioxane (568.06): C, 50.75; H, 7.04; N, 9.86; Cl, 8.11. Found: C, 51.03; H, 6.93; N, 9.46; Cl, 7.85.

EXAMPLE 26

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(3,5-dimethoxyanilino)carbonylamino-3-amino]propionic acid • HCl (26)

Compound **26**, prepared by reacting 3,5-dimethoxyphenylisocyanate (10.2 mmol) with AH2 (10.2 mmol) as shown in Example 22, was isolated as a white powder (1.89 g): mp 190-193°C; MS m/e 534 (MH+). Anal. calcd. for $C_{26}H_{39}N_5O_7$ • 1.2 HCl • 0.2 Dioxane (585.40): C, 53.35; H, 7.20; N, 11.96; Cl, 7.27. Found: C, 53.48; H, 7.38; N, 12.05; Cl, 6.97.

EXAMPLE 27

N-[(4,4'-Bipiperidin-1-yl-)carbonyl]-R-(-)-nipecotyl-[(S)-3-amino-3-(3-pyridyl)]propionic acid • 3HCl (27)

Intermediate AJ1 (5.5 mmol), prepared as shown in Example 16, was dissolved in DCM (140 mL), cooled (5°C), treated with *p*-nitrophenylchloroformate (5.5 mmol) and (16.5 mmol), and stirred for 2 h. The mixture was diluted with water (15 mL), the layers separated, and the organic layer dried and evaporated to an oil. The oil was dissolved in MeCN (70 mL), treated with N-Boc-4,4'-bipiperidine (7.5 mmol) and DMAP (5.5 mmol), and heated at reflux for 24 h. The mixture was cooled, evaporated to a solid, and partitioned between EtOAc (150 mL) and NaOH (1 *N*, 20 mL). The layers were separated, and the organic layer dried, evaporated to a solid, and purified by silica gel chromatography (8% EtOH/DCM) to give green glass AJ2 (1.5 mmol). AJ2 was saponified and deprotected as described in Example 16 to give **27** as a pale yellow powder (0.73 g): mp 121-125°C; MS m/e 472 (MH+). Anal. calcd. for $C_{25}H_{37}N_5O_4$ • 3.6 HCl • 1.0 Dioxane (690.98): C, 50.41; H, 7.09; N, 10.14; Cl, 18.47. Found: C, 50.80; H, 7.31; N, 10.20; Cl, 18.78.

EXAMPLE 28

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(2-naphthylamino)carbonylamino-3-amino]propionic acid • HCl (28)

Compound **28**, prepared by reacting 2-naphthylisocyanate (8.5 mmol) with AH2 (8.5 mmol) as shown in Example 22, was isolated as a white powder (1.65 g): mp 187-193°C; MS m/e 524 (MH+). Anal. calcd. for $C_{28}H_{37}N_5O_5$ • 1.36 HCl • 0.72 Dioxane (602.07): C, 55.86; H, 7.39; N, 11.63; Cl, 8.01. Found: C, 56.03; H, 7.11; N, 11.23; Cl, 7.97.

EXAMPLE 29

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-aminomethyl-5-(S)-(3-N-benzyl)imidazoline-2,4-dione • HCl (29)

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(2-benzylamino)carbonylamino-3-amino]propionic acid hydrochloride (0.15 g), prepared from intermediate AH2 (4.4 mmol) and benzylisocyanate (4.4 mmol) as described in Example 22, was dissolved in aq. HCl (3 *N*) and stirred for 18 h at RT. This solution was concentrated *in vacuo* to give a white solid. This solid was triturated and dried to give **29** as a white foam (0.144 g): ^{1}H NMR (DMSO-d_6) δ 9.0 (m, 1 H), 8.6 (m, 1 H), 8.3 (m, 1 H), 7.2 (m, 5 H), 4.48 (s, 2 H), 4.2 (m, 2 H), 3.7 (m, 1 H), 3.4 (m, 1 H), 3.2 (d, 3 H), 2.7 (d, 3 H), 2.2 (m, 3 H), 1.7 (m, 3 H), 1.0-1.6 (m, 10 H); MS m/e 470 (MH+).

EXAMPLE 30

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(2-phenethylamino)carbonylamino-3-amino]propionic acid • HCO_2H (30)

Compound **30**, prepared by reacting 2-phenethylisocyanate (4.1 mmol) with AH2 (4.1 mmol) as shown in Example 22, was isolated as a tan foam (0.41 g): mp 65-72°C; MS m/e 502 (MH+). Anal. calcd. for

$C_{26}H_{39}N_5O_5$ • 1.2 HCO_2H • 1.0 H_2O (574.87): C, 56.83; H, 7.61; N, 12.18. Found: C, 57.12; H, 7.80; N, 11.85.

6-Methyl-3-pyridine-carboxaldehyde (AK2)

Aldehyde precursor AK2 was prepared in two steps using standard conditions. AK1 (0.066 mol) was dissolved in THF (100 mL), cooled (-78°C), treated with $LiAlH_4$ (0.066 mol), and stirred for 4 h. The reaction was quenched with sat'd NH_4Cl, warmed, filtered with $CHCl_3$ washes (250 mL), and the layers separated. The organic layer was dried and evaporated to give a clear oil (0.054 mol). The oil was dissolved in DCM (200 mL), treated with MnO_2 (70 g), and heated at reflux for 6 h. The mixture was cooled, filtered, and the solvent evaporated to give AK2 (0.052 mol) as a brown oil.

EXAMPLE 31

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-3-amino-3-(6-methyl-3-pyridyl)] propionic acid • 2HCl (31)

Compound **31**, prepared as described in Example 16 starting with Boc-R-nipecotic acid (6.9 mmol) and methyl (S)-3-amino-3-(6-methyl-3-pyridyl)propionate (see examples AK5, AG5; 6.9 mmol). Compound **31** was isolated as a white foam (1.20 g): mp 99-105°C; MS m/e 431 (MH+). Anal. calcd. for $C_{23}H_{34}N_4O_4$ • 2.24 HCl • 1.0 H_2O • 0.24 Acetonitrile (534.33): C, 51.70; H, 7.35; N, 11.11; Cl, 14.82. Found: C, 51.32; H, 7.45; N, 11.23; Cl, 14.42.

EXAMPLE 32

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-3-amino-3-(5-bromo-3-pyridyl)] propionic acid • 2HCl (32)

Compound **32**, prepared as described in Example 16 starting with Boc-R-nipecotic acid (4.8 mmol) and methyl 3-S-amino-3-(5-bromo-3-pyridyl)propionate (see examples AK5, AG5; 4.8 mmol), was isolated as a white foam (1.24 g): mp 98-101°C; MS m/e 496 (MH+). Anal. calcd. for

$C_{22}H_{31}BrN_4O_4 \cdot 2.2\ HCl \cdot 1.0\ H_2O$ (593.67): C, 44.51; H, 5.98; N, 9.44; Cl, 13.14. Found: C, 44.17; H, 6.37; N, 9.81; Cl, 13.10.

EXAMPLE 33

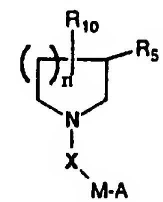
N-3-(4-Formamidinopiperidinepropionyl)-R-(-)nipecotyl-[(S)-3-amino-3-(3-pyridyl)] propionic acid • 2HCl (33)

Formamidine **33** was prepared according to the procedure of M. K. Scott (*J. Med. Chem.* **1983**, *26*, 534) as shown in Scheme AL. Intermediate AL1 (see Example 21; 2.3 mmol) was dissolved in EtOH (20 mL), treated with ethyl formimidate•HCl (3.7 mmol), stirred for 22 h, and filtered. The filtrate was treated with Et_2O (40 mL), cooled in an ice bath, and filtered to give glassy AL2. AL2 was dissolved in aq. HCl (4 *N*, 15 mL), stirred for 28 h, and evaporated to give **33** as a white foam (0.75 g): mp 49-55°C. ^1H NMR (DMSO-d_6) δ 9.35 (s, 1 H), 9.1 (m, 2 H), 8.8 (m, 2 H), 8.70 (d, 1 H), 8.5 (m, 1 H), 7.8 (m, 2 H), 5.2 (dd, 1 H), 4.2 (m, 1 H), 3.8 (m, 2 H), 3.2 (m, 2 H), 2.8 (m, 2 H), 2.6 (m, 1 H), 2.3 (m, 2 H), 1.8 (m, 3 H), 1.0-1.7 (m, 12 H); MS m/e 444 (MH+).

[DIP-J Classic の試用モードでダウンロードされました]

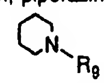
WE CLAIM:

1. A compound represented by the general formula (I):



(I)

wherein M is $(CH_2)_m$ or piperidin-1-yl;

wherein A is selected from any of piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, NHR^2, or  wherein R_9 is selected from any of H, alkyl, CH(NH), CMe(NH) or acyl;

wherein R_{10} is H or $C(O)N(R^1)YZ$

wherein R_1 is selected from H or cycloalkyl;

wherein R^2 is selected from any of H, alkyl or acyl;

wherein R_5 is H or $C(O)NHQ(CHW)_rCO_2R_8$; wherein Q is selected from CH_2, CH-aryl, CH-heteroaryl, CH-substituted-heteroaryl or CH-alkyl; W is selected from H or $N(R_6)T\text{-}R_7$, wherein R_6 is selected from any of H, alkyl or acyl, T is selected fron C(O), C(N-CN) or SO_2, and R_7 is selected from any of alkyl, aryl, aralkyl, alkoxy, or aminoalkyl; and R_8 is selected from H, alkyl or aralkyl.

wherein m is the integer 1, 2, or 3;

wherein X is selected from any of C(O), C(O)O, C(O)NH, CH_2, or SO_2;

wherein n is the integer 1, 2, or 3;

wherein r is 0 or 1;

wherein R^1 is selected from H or cycloalkyl;

wherein Y is selected from any of $(CH_2)_p$, $CH(R^3)(CH_2)_q$, $(CH_2)_qCH(R^3)$, $(CH(COR^4)CH_2)_q$, $(CH_2)_qCHOH$ or piperidine-3-carboxylic acid; with the proviso that when Y is $(CH_2)_p$ and p is 2, X is other than C(O) or when X is C(O) then either R^1 is other than H or R^2 is other than H, and with the proviso that when Y is $(CH(CO_2R^4)CH_2)_q$ X is other than C(O) or CH_2;

wherein p is 2 or 3;

wherein q is 1, 2, or 3;

wherein R^3 is alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, aralkyl or heteroaryl;

wherein R^4 is H or alkyl or cycloalkyl;

wherein Z is CO_2H, CO_2alkyl, SO_3H, PO_3H_2 , or 5-tetrazole; provided that at least one of R_5 and R_{10} is hydrogen;

or the enantiomer or the pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R_5 is H, R_{10} is H or $C(O)N(R^1)YZ$, M is $(CH_2)_m$ and A is selected from any of piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl or NHR^2.

3. The compound of claim 1, wherein R_5 is H and R^2 is hydrogen.

4. The compound of claim 1, wherein R_5 is H and m is 1or 2.

5. The compound of claim 1, wherein R_5 is H and X is C(O).

6. The compound of claim 1, wherein R_5 is H and R^1 is hydrogen.

【DIP-J Classic の試用モードでダウンロードされました】

7. The compound of claim 1, wherein R_5 is H and Y is 4-oxo-nipecotic acid.

8. The compound of claim 1, wherein R_5 is H and q is 1.

9. The compound of claim 1, wherein R_5 is H and R^3 is aryl.

10. The compound of claim 1, wherein R_5 is H and R^4 is hydrogen.

11. The compound of claim 1, wherein R_5 is H and Z is CO_2H.

12. The compound of claim 1, wherein the group $C(O)N(R^1)YZ$ is attached at the 3- or 4-position of the central azacycle.

13. The compound of claim 1, wherein the group $C(O)N(R^1)YZ$ is attached at the 3-position of the central azacycle.

14. The compound of claim 1, selected from any of:

N-3-(4-Piperidinepropionyl)-nipecotyl-(3-amino-3-phenyl) propionic acid

N-(4-Piperidinemethylaminocarbonyl)-nipecotyl-(3-amino-2-methyl) propionic acid

N-(4-Piperidinemethyloxycarbonyl)-nipecotyl-D-aspartic acid α-methyl ester

N-3-(4-Piperidinepropionyl)-pyrrolidine-3-carboxy-[3-amino-3-(4-tolyl)] propionic acid

N-3-(4-Piperidinepropionyl)-isonipecotyl-(3-amino-3-methyl) propionic acid

N-3-(4-Piperidinepropionyl)-isonipecotyl-[3-amino-3-(4-carboxyphenyl)] propionic acid

N-3-(4-N-Methyl-piperidinepropionyl)-nipecotyl-3-aminopropionic acid

N-3-(4-Piperidinepropionyl)-nipecotyl-4-oxonipecotic acid

N-3-(4-Piperidinepropionyl)-nipecotyl-[3-amino-3-(2-trimethylsilylethynyl)] propionic acid

N-(6-Aminocaproyl)-nipecotyl-3-âmino-3-(3-pyridyl)propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-(3-amino-2-hydroxy) propionic acid

N-3-(4-Piperidineethanesulfonyl)-nipecotyl-3-aminopropionic acid

N-3-(4-Piperidinepropionyl)-nipecotyl-5H-(2-aminoethyl)tetrazole

N-3-(4-N-Methyl-piperazinepropionyl)-nipecotyl-[3-amino-3-(3,4-methylenedioxyphenyl)]propionic acid

N-3-(4-N-Methyl-piperazinepropionyl)-nipecotyl-[3-amino-3-(3,-quinolinyl)]propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-[(S)-3-amino-3-(3,4-methylenedioxyphenyl)]propionic acid

N-3-(4-Piperidinepropionyl)-hexahydroazepine-3-carboxy-[3-amino-3-(3-quinolinyl)]propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-[(S)-3-amino-3-(3-quinolinyl)]propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-[(S)-3-amino-3-(2-*t*-butylethynyl)] propionic acid

N-3-(4-Piperidinepropyl)-nipecotyl-[(S)-3-amino-3-(3,4-methylenedioxyphenyl)]propionic acid, and

N-3-(4-Piperidinepropionyl)-R-(-)-nipecotyl-[(S)-3-amino-3-(3-pyridyl)] propionic acid.

[DIP-J Classic の試用モードでダウンロードされました]

15. The compound of claim 1, wherein R_{10} is H, R_5 is H or $C(O)NHQ(CHW)_rCOOR_8$, M is piperidin-1-yl and A is  R_9.

16. The compound of claim 1, wherein R_{10} is H and X is C(O).

17. The compound of claim 1, wherein R_{10} is H and Q is (CH_2).

18. The compound of claim 1, wherein R_{10} is H and W is $N(R_6)$-T-R_7.

19. The compound of claim 1, wherein R_{10} is H and T is C(O).

20. The compound of claim 1, wherein R_{10} is H and R_9 is H.

21. The compound of claim 1, wherein R_{10} is H and R_8 is H.

22. The compound of claim 1, wherein R_{10} is H and R_7 is $NH(CH_2)_2Ph$.

23. The compound of claim 1, wherein R_{10} is H and R_7 is H.

24. The compound of claim 1, wherein n is 2.

25. The compound of claim 1, selected from any of:

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(3-methoxyanilino)carbonylamino-3-amino]propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-benzyloxycarbonylamino-3-amino]propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(3-chlorobenzyloxy)carbonylamino-3-amino]propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-benzylsulfonylamino-3-amino]propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(3,5-dimethoxyanilino)carbonylamino-3-amino]propionic acid

N-[(4,4'-Bipiperidin-1-yl-)carbonyl]-R-(-)-nipecotyl-[(S)-3-amino-3-(3-pyridyl)] propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(2-naphthylamino)carbonylamino-3-amino]propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-aminomethyl-5-(S)-(3-N-benzyl)imidazoline-2,4-dione • HCl

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-2-(2-phenethylamino)carbonylamino-3-amino]propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-3-amino-3-(6-methyl-3-pyridyl)] propionic acid

N-3-(4-Piperidinepropionyl)-R-(-)nipecotyl-[(S)-3-amino-3-(5-bromo-3-pyridyl)] propionic acid, and

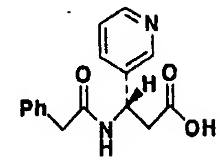
N-3-(4-Formamidinopiperidinepropionyl)-R-(-)nipecotyl-[(S)-3-amino-3-(3-pyridyl)] propionic acid.

26. A composition for treating platelet-mediated thrombotic disorders comprising the compound of Claim 1 in an effective amount for treating such disorders in combination with a pharmaceutically acceptable carrier.

27. A method of treating platelet-mediated thrombotic disorders comprising administering to a patient afflicted with such disorder an effective amount of the compound of Claim 1 to treat such disorder.

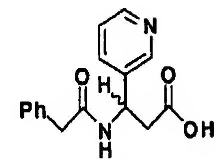
28. The method of Claim 17, wherein the amount is 0.1-300 mg/kg/day.

29. A process for preparing a compound of the formula AG4



AG4

comprising treating a compound of the formula AG3

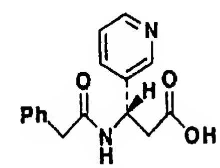


AG3

with penicillin amidase.

30. The process of claim 19, wherein the compound of the formula AG3 was placed in a water solution and the pH was adjusted to about 7.5 prior to treatment with penicillin amidase.

31. A compound of the formula AG4:



AG4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/07130

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/60 C07D401/06 C07D401/12 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 08536 A (FUJISAWA PHARMACEUTICAL CO ;OHKUBO MITSURU (JP); TAKAHASHI FUMIE ()) 30 March 1995 see claim 1; examples	1-28
X	WO 95 25091 A (ORTHO PHARMA CORP) 21 September 1995 see claim 1; examples	1-28
X	J. MED. CHEM. (1995), 38(10), 1582-92 CODEN: JMCMAR;ISSN: 0022-2623, 1995, XP000572765 HOEKSTRA, WILLIAM J. ET AL: "Design and Evaluation of Nonpeptide Fibrinogen.gamma. Chain-Based GPIIB/IIIA Antagonists" see the whole document	1-28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 1997	03.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/07130

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0 725 059 A (SUMITOMO PHARMA) 7 August 1996 see claim 1; examples	1-28
P,X	BIOORG. MED. CHEM. LETT. (1996), 6(20), 2371-2376 CODEN: BMCLE8;ISSN: 0960-894X, 16 October 1996, XP002039034 HOEKSTRA, WILLIAM J. ET AL: "Solid-phase parallel synthesis applied to lead optimization: discovery of potent analogs of the GPIIb/IIIa antagonist RWJ-50042" see the whole document	1-28
P,X	WO 96 29309 A (FUJISAWA PHARMACEUTICAL CO ;OHKUBO MITSURU (JP); TAKAHASHI FUMIE ()) 26 September 1996 see claim 1; examples	1-28

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

2

In ational application No.
PCT/US 97/07130

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-11, 15-24
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims 1-11, 15-24 are so broad that a complete search is not possible on economic grounds (PCT-Art. 17.2a)

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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